Society of Biological Psychiatry 2010 Annual Meeting

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THURSDAY, MAY 20

PLENARY SESSION
Depression
Thursday, May 20, 2010 8:00 AM - 10:15 AM
Location: Grand Ballroom ABC
Chair: J. John Mann

1. Antidepressant Action: From Molecule to Mouse to Man

Randy Blakely

Vanderbilt University, Nashville, TN

Dr. Blakely is the Allan D. Bass Professor of Pharmacology & Psychiatry at the Vanderbilt University School of Medicine. He also directs the Vanderbilt Center for Molecular Neuroscience, the Vanderbilt/NIMH Silvio O. Conte Center for Neuroscience Research, and the Vanderbilt/NIMH Postdoctoral Training Program in Neurogenomics. Dr. Blakely received a B.A *summa cum laude* in Philosophy from Emory University and a Ph.D. in Neuroscience from the Johns Hopkins School of Medicine, studying with Dr. Joseph Coyle. His postdoctoral training at the Yale/HHMI Center for Molecular Neuroscience with Dr. Susan Amara led to the cloning and molecular characterization of multiple neurotransmitter transporters, including the antidepressant-sensitive norepinephrine and serotonin transporters. For the past 20 years, Dr. Blakely's laboratory has studied the genetics, structure, regulation and pathophysiology of these and other synaptic transporters, authoring over 200 publications. Dr. Blakely's research and mentorship have garnered multiple honors including the Daniel Efron Award from the ACNP, a Distinguished Investigator Award from NARSAD, a MERIT Award from the NIMH, a Zenith Award from the Alzheimer's Association and the Julius Axelrod Award from ASPET. In 2010, Dr. Blakely was selected as a Fellow of the American Acadamy for the Advancement of Science.

2. The Cognitive Control of Emotion: From Basic Mechanisms to Mechanistic Breakdowns

Kevin Ochsner

Psychology, Social Cognitive Neuroscience Lab, Columbia University, New York, NY

Kevin Ochsner Is Associate Professor of Psychology at Columbia University. Dr. Ochsner graduated *summa cum laude* from the University of Illinios where he received his B.A. in Psychology. He then received a M.A. and Ph.D. in psychology from Harvard University working in the laboratory of Dr. Daniel Schacter, where he studied emotion and memory. Also at Harvard, he began his postdoctoral training in the lab or Dr. Daniel Gilbert, where he first began integrating social cognitive and neuroscience approaches to emotion-cognition interactions, and along with Matthew Lieberman published the first articles on the emerging field of Social Cognitive Neuroscience. Dr. Ochsner later completed his postdoctoral training at Stanford University in the lab of Dr. John Gabrieli, where in collaboration with Dr. James Gross he conducted some of the first in functional neuroimaging studies examining the brain systems supporting cognitive forms of emotion regulation. He is now director the Social Cognitive Neuroscience Laboratory, where current studies examine the psychological and neural bases of emotion, emotion regulation, and empathy in both healthy and clinical populations. Dr. Ochsner has received various awards for his research and teaching, including the American Psychological Association's Division 3 New Investigator Award, the Cognitive Neuroscience Society's Young Investigator Award, and Columbia University's Lenfest Distinguished Faculty Award.

3. Theory to Practice: Towards the Use of Neuroimaging in the Diagnosis and Management of Patients with Major Depression

Helen Mayberg

Psychiatry, Emory University, Atlanta, GA

Dr. Mayberg is Professor of Psychiatry and Neurology, and the Dorothy C. Fuqua Chair in Psychiatric Imaging and Therapeutics at the Emory University School of Medicine where she has an active research program in the neuroimaging of depression. Her group's studies over the past 20 years have systematically examined depression pathophysiology in both psychiatric and neurological patients, as well as mechanisms mediating antidepressant response to various modes of treatments. This long-term interest in neural network models of mood regulation in health and disease led to the development of a new intervention for treatment resistant patients using deep brain stimulation, a continued focus on ongoing research. Current projects also emphasize development of imaging biomarkers predictive of treatment response and optimal treatment selection for individual depressed patients at all stages of illness. Dr. Mayberg is a Board Certified Neurologist, trained at Columbia's Neurological Institute in New York, with fellowship training in nuclear medicine at Johns Hopkins. She received a BA in Psychobiology from UCLA and an MD from University of Southern California. She is an active member of the Institute of Medicine, the NARSAD Scientific Advisory Board, the Society for Neuroscience, the American Neurological Association, the Organization for Human Brain Mapping, the American College of Neuropsychopharmacology and the Society of Biological Psychiatry. Her research program has ongoing funding from the NIMH, the Stanley Medical Research Institute, the Dana Foundation, NARSAD and the Woodruff Fund.

PRESIDENTIAL INVITED LECTURE
Thursday, May 20, 2010 10:45 AM - 11:45 AM
Location: Grand Ballroom ABC
Chair: Stephan Heckers

4. Future Perspectives of Depression Research

Florian Holsboer

Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany

Professor Florian Holsboer is Director of the Max Planck Institute of Psychiatry in Munich since 1989. This is a research institute with over 600 employees that work in 5 research wards with 120 beds for neurological and psychiatric patients and two outpatient clinics for 34 patients. In addition, the Institute has 10 clinical research groups and about 20 basic research groups including

0006-3223/10/$36.00

human and mouse genetics, transcriptomics, proteomics, metabolomics, molecular pharmacology, neuroimaging and behavioral neurobiology.
Professor Holsboer has made hallmark contributions to the endocrinology of depression and to the characterization of patients with affective disorders using genetic, neuroendocrine, sleep-EEG and imaging methods. His contributions include among others a classical paper on an endocrine challenge test designed for assessment of stress system hyperactivity in depressed patients (the so-called DEX-CRH test) which by now is an established biomarker to predict the course of depression. This test was based on the corticosteroid receptor hypothesis of depression, formulated and published in 2000. The Holsboer group was also the first to report the generation of CRH-1 receptor knock out mice and derived from these and other findings that those depressed patients oversecreting CRH in the brain would benefit from a CRH-R1 receptor antagonist. He also was the first to report clinical and sleep-EEG findings from depressed patients treated with a CRH-R1 antagonist. Based on clinical and animal experiments and employing molecular techniques he made plausible that anti-depressants operate through recovery of a hyperactive stress system. Holsboer's research is fundamental for the concept that targeting aberrant stress hormone regulation is a worthwhile strategy to hasten the onset of anti-depressant action. His research group demonstrated that polymorphisms in the gene coding for FKBP5, that regulates glucocorticosteroid receptor function, were found to predict accelerated response to antidepressant treatment. Holsboer is a pioneer in the field of personalized medicine and the knowledge that emerged from this research proved valuable in delineating new strategies for both drug discovery and establishing endophenotypes for psychiatric genetics. He is currently expanding the approach to pharmacogenomics of depression and multiple sclerosis and was able to show that gene variants are indeed capable to assist differential therapy in these diseases.
Dr. Holsboer has published more than 800 scientific papers and is leading the citation list of neuroscientists in Germany. According to ISI he is among the 250 most cited neuroscientists worldwide. His work has been recognized by numerous prizes, most recently the Anna Monika Prize in 2003, the BMS Freedom to Discover Award 2004, the Neuropsychopharmacology Award 2006, the Aschoff-Medal in 2008, and the K.J.-Zülch-Prize in 2009. He received the Doctor Honoris Causa from the University of Leiden in 2008. In addition to numerous societies Dr. Holsboer is member of the American College of Neuropsychopharmacology, the Society of Biological Psychiatry and the Society of Neuroscience. He is honorary member of the American College of Psychiatrists.

SYMPOSIUM

Molecular Mechanisms Linking Serotonin Neurotransmission to Behaviors in Depression

Thursday, May 20, 2010 12:30 PM - 2:30 PM
Location: Grand Couteau - 5th Floor
Chair: Xiaohua Li*
Co-Chair: Gwenn S. Smith**

*Supported by R01MH073723, K02MH086622
**Supported by NIH/NIMH 62823, 01623

5. P11 Interaction with Serotonin Receptors and its Role in Depression

Per Svenningsson

Karolinska Institute, Sweden

Background: The molecular mechanisms whereby serotonin receptors regulate depression-like states could involve plastic changes in modulatory adaptor proteins.
Methods: Yeast two hybrid screend were used to identify serotonin receptor interacting proteins. P11 KO mice were generated by replacing the first coding exon with a NEO cassette. Standard biochemical, histological and behavioural tests were used to study p11 KO mice.
Results: 5-HT1B and 5-HT4 receptors interact with the adaptor protein, p11. p11 expression is increased in the rodent brain after antidepressant therapies. Conversely, there is a decreased level of p11 in a genetic animal model of depression and brain tissue from depressed patients. Overexpression of p11 increases 5-HT1B and 5-HT4 receptor function in cells and recapitulates certain actions of antidepressant drugs in behavioral paradigms in mice. p11 knockout (KO) mice have reduced responsiveness to stimulation of 5-HT1B and 5-HT4 receptors and to behavioral actions of imipramine. Using a common animal model of Parkinson´s Disease, unilaterally 6-OHDA-lesioned p11 WT and KO mice, have also demonstrated that administration of a selective 5-HT1B receptor agonist, CP94253, inhibited L-DOPA-induced rotational behavior and abnormal involuntary movements in a p11-dependent manner.
Conclusions: p11 influences several 5-HT1B and 5-HT4 receptor-mediated actions particularly in depression- and Parkinsonian-like disease states.
Supported by Swedish Medical Research Council

6. Role of GSK-3 Signaling in Serotonergic Behaviors and the Effects of Mood Stabilizers

Martin Beaulieu

Universite Laval Robert Giffard, Canada

Background: Drugs regulating brain serotonin (5-HT) neurotransmission are used for the management of mental conditions such as depression, anxiety and bipolar disorder. However, the molecular mechanisms by which 5-HT is involved in the regulation of aberrant emotional behaviors are poorly understood. Antidepressant and drugs like lithium that affect mood without clearly involving 5-HT neurotransmission share the common characteristic of inhibiting glycogen synthase kinase 3 (GSK3) mediated cell signaling.
Methods: We generated knockin mice expressing a mutant form of Tryptophan hydoxylase 2 (Tph2) --major rate limiting enzyme for brain 5-HT synthesis--that was identified in humans with mood disorders. The effects of this mutation on behavior and GSK3 signaling were evaluated. Knockin mice were also bred with mice displaying altered GSK3 signaling responses to evaluate the contribution of this signaling pathway in the regulation of behavior by 5-HT.
Results: Expression of mutant Tph2 in mice results in a reduction of about 80% in brain 5-HT production and leads to behavioral abnormalities in tests assessing 5-HT-mediated mood related behaviors in rodents. Reduction in brain 5-HT levels is accompanied by activation of GSK3. Importantly, inactivation of GSK3 in Tph2 knockin mice alleviates the aberrant behaviors produced by 5-HT deficiency.
Conclusions: These findings identify GSK3 signaling as an important pathway through which brain 5-HT regulates mood related behaviors. Targeting GSK3 and related signaling events may afford therapeutic advantages for the management of certain 5-HT-related psychiatric conditions.
Supported by NARSAD, CIHR

7. Regulation of Stress-Responsive FoxO by Serotonin and Antidepressant

Xiaohua Li

University of Alabama at Birmingham

Background: The mammalian forkhead "O" (FoxO) is a family of transcription factors that responds both to growth factors that inactivate FoxO and to stress signals that activate FoxO. In response to mood-regulating neurotrophins, FoxO is transported out of nucleus and inactivated via Akt-dependent phosphorylation. We hypothesized that FoxO is a transcriptional mediator in stress-induced depression. In this study, we investigated the impact of FoxO in animal models of depression.

Methods: C57BL/6 wild-type mice were used to test the response of brain FoxO to learned helpless stress-induced depression. FoxO knockout mice were used to examine the role of FoxO in several depression- and anxiety-related behavioral tests. D-fenfluramine was administered to mice to test the effect of serotonin on phosphorylation and nuclear/cytosolic distribution of brain FoxO. The response of FoxO to pharmacological treatments was tested *in vitro* and in mice.
Results: When wild-type mice were subjected to the learned helplessness paradigm, the nuclear FoxO was significantly increased, indicating increased activity. FoxO3a-deficient mice had less depression-like behaviors, whereas neuronal FoxO1 knockout mice exhibited lower anxiety-like behavior. The serotonin enhancer d-fenfluramine increased the inhibitory phosphorylation and reduced the nuclear contents of FoxO in mouse brain, and the effect was mediated by the PI3K/Akt signal pathway. Importantly, FoxO activity was reduced by both chronic imipramine and lithium treatment.
Conclusions: The serotonin- and neurotrophin-regulated FoxO is a stress-responsive transcription factor. Pharmacological control of brain FoxO activity or modulation of its signal pathways may have therapeutic implication in depression.
Supported by R01MH73723

8. Molecular Imaging of Serotonin Function in Geriatric Depression

Gwenn S. Smith

Johns Hopkins University School of Medicine, Baltimore, MD

Background: The evidence implicating the role of the serotonin system in mood disorders, as well as neurogenesis, provides a compelling rationale for the study of the serotonin system in geriatric depression. Positron emission tomography (PET) molecular imaging methods represents a unique opportunity to test hypotheses generated from animal models to geriatric mood disorders.
Methods: PET studies of the cerebral metabolic response to citalopram, as well as occupancy of the serotonin transporter (SERT, [11C]-DASB).
have been performed in unmedicated, geriatric depressed patients.
Results: Cerebral glucose metabolism was decreased during citalopram treatment in the right anterior cingulate (BA 24), superior and middle frontal (bilaterally) and right inferior frontal, superior and middle temporal (bilaterally) and left inferior temporal gyri, precuneus and posterior cingulate (bilaterally), midbrain (bilaterally), right pons, parahippocampal gyrus and amygdala (bilaterally). Increased metabolism was observed in the putamen (bilaterally), right thalamus (pulvinar and medial dorsal nuclei), inferior parietal lobule (bilaterally) occipital (right cuneus and left middle and inferior occipital gyri) and cerebellum (bilaterally).Voxel-wise analyses of the parametric [^{11}C]-DASB images showed significant SERT occupancy (70% or greater), as well as correlations between SERT occupancy and mood symptom improvement. The regions of significant correlation are similar to the regions of metabolic decrease (anterior cingulate, middle frontal, superior and middle temporal gyri, precuneus, parahippocampal gyrus) and increase (inferior parietal lobule, cuneus) by citalopram.
Conclusions: A serotonergic mechanism may underlie the functional neuroanatomic changes associated with geriatric depression and the affective and cognitive responses to treatment.
Supported by NIH/NIMH 64823

SYMPOSIUM
The Emerging Neurobiology of Antidepressant Treatment Response

Thursday, May 20, 2010 12:30 PM - 2:30 PM
Location: Grand Chenier - 5th Floor
Chair: Katharina Domschke
Co-Chair: Yvette Sheline*

*Supported by NIMH:2k24MH79510 and 2RO1MH64821

9. Connectivity of the Subgenual Cortex and HPA Axis in Depression

Alan F. Schatzberg[1], Jennifer Keller[2], Keith Sudheimer[2], Michael Greicius[2]

[1]Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, [2]Stanford University, Stanford, CA

Background: Our group has reported, using a resting-state fMRI approach, that subgenual cingulate connectivity, within a posterior cingulate-hippocampal-medial prefrontal network, is increased in a mixed group of delusional and nondelusional depressives compared to healthy controls. The subgenual region has been thought to participate in a circuit that involves anterior and posterior cingulate and prefrontal cortex as well as the hypothalamus.
Methods: Herein, we report on the relationship of resting-state functional connectivity in the subgenual region to activity of the hypothalamic-pituitary-adrenal (HPA) axis in 60 patients with major depression (30 delusional and 30 nondelusional) as well as 30 healthy controls. Patients were assessed for serum cortisol and ACTH activity on an hourly basis beginning at 6 p.m. and ending at 9 a.m. in a G-CRC setting. MRI's were obtained after completing blood collections.
Results: Data are presented on the relationship of mean cortisol levels from 6 p.m. to 1 a.m. and from 1 a.m. to 9 a.m. with connectivity profiles of the subgenual region. We also present data on the relationship between hippocampal connectivity and the HPA axis. Implications of these data for understanding a key circuit involved in the pathogenesis of depression are discussed.
Conclusions: Resting-state *f*MRI can identify abnormalities in brain connectivity in depression and relationships with elevated HPA axis activity.
Supported by RO1 MH50604

10. Prediction of Antidepressant Treatment Response - A Pharmaco- and Imaging Genetic Contribution

Katharina Domschke[1], Udo Dannlowski[2], Patricia Ohrmann[2], Christa Hohoff[2], Jürgen Deckert[3], Volker Arolt[2], Thomas Suslow[2], Bernhard T. Baune[4]

[1]Department of Psychiatry, University of Muenster, [2]Department of Psychiatry, University of Muenster, Muenster, Germany, [3]Department of Psychiatry, University of Wuerzburg, Wuerzburg, Germany, [4]Department of Psychiatry, James Cook University, Townsville, Australia

Background: In major depression, an increasing number of pharmacogenetic studies have examined association of antidepressant treatment response with variation in candidate genes. Given only few consistently reproducible findings, we attempted to further refine investigation of the clinical phenotype of depression in pharmacogenetic studies with particular attention to gender,

melancholic and anxious depression as well as the intermediate phenotype of emotional processing.
Methods: In a sample of 256 Caucasian patients with Major Depression, candidate gene variants of the serotonergic, noradrenergic, NPY and endocannabinoid systems were investigated for their impact on antidepressant treatment response. A subsample of 35 patients was additionally scanned by means of fMRI at 3 T under visual presentation of emotional faces using an imaging genetics approach.
Results: The MAO-A VNTR and the COMT val158met variants were found to influence antidepressant treatment response specifically in female patients. The 5-HT1A -1019 C/G polymorphism was associated with treatment response in patients with melancholic, but not atypical depression. 5-HTTLPR, CNR1 rs1049353 and NPY rs16147 were observed to significantly impair treatment response particularly in anxious depression via altered brain activity in amygdala, prefrontal and striatal regions during processing of depression-related emotional stimuli.
Conclusions: The present results suggest a significant impact of 5-HTT, 5-HT1A, MAO-A, COMT, CNR1 and NPY gene variants on antidepressant treatment response with differential effects regarding gender and clinical subtypes of melancholic and anxious depression, potentially mediated via distorted emotional processing in the limbic-frontal circuit. These findings point towards a network model of cellular (genetic) and circuit (brain network) factors contributing to antidepressant treatment success.

11. The Role of the Default Mode Network (DMN) in Understanding Emotional Circuitry in MDD Pre- and Post- Antidepressant Treatment

Yvette Sheline[1], Marcus E. Raichle[2], Mark A. Mintun[2], Abraham Z. Snyder[2], Deanna Barch[3]

[1]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, [2]Department of Radiology, Washington University School of Medicine, St. Louis, MO, [3]Department of Psychology, Washington University School of Medicine, St. Louis, MO

Background: The recently discovered default mode network (DMN) is a group of areas in the human brain characterized, collectively, by functions of a self-referential nature. In normal individuals activity in the DMN is reduced during non-self-referential goal directed tasks, in keeping with the folk-psychological notion of losing one's self in one's work. Imaging and anatomical studies in major depression have found alterations in both the structure and function in some regions that belong to the DMN suggesting a basis for the disordered self-referential thought of depression.
Methods: Here we sought to examine DMN functionality as a network in patients with major depression, asking whether the ability to regulate its activity and, hence, its role in self-referential processing was impaired. To do so we asked patients and controls to examine passively negative pictures as well as actively re-appraise them.
Results: In widely distributed elements of the DMN--ventromedial prefrontal cortex (BA 10), anterior cingulate (BA 24/32), lateral parietal cortex (BA 39) and lateral temporal cortex (BA 21)-- depressed, but not control subjects, exhibited a failure to reduce activity while both looking at negative pictures and reappraising them. Further, looking at negative pictures elicited a significantly greater increase in activity in other DMN regions (amygdala, parahippocampus and hippocampus) in depressed than in control subjects.
Conclusions: These data suggest depression is characterized by both stimulus-induced heightened activity as well as a failure to normally down-regulate activity broadly within the DMN. These findings provide a brain network framework within which to consider the pathophysiology of depression.
Supported by NIMH: 2K24MH79510 and 2R01MH64821

12. From Resetting Chemical Dysbalance to Modulating Networks - Lessons on the Neurobiology of Treatment Resistant Depression from Deep Brain Stimulation

Thomas E. Schlaepfer[1,2]

[1]University of Bonn, Bonn, Germany, [2]The Johns Hopkins University, Baltimore, MD

Background: Deep brain stimulation (DBS) is a procedure that referring to stereotactic placement of electrodes in a given brain region with electrodes connected to a neurostimulator implanted under the skin of the chest. It is a FDA approved method for control of severe forms of tremor in Parkinson's disease, essential tremor and primary dystonia. Recently, it has been proposed as a treatment in treatment resistant major depression. It might be, that more focused, targeted treatment approaches modulating well defined targets within affective networks will prove a more effective approach to help treatment-resistant patients.
Methods: We assessed antidepressant effects of bilateral DBS to the nucleus accumbens in fourteen patients suffering from treatment resistant depression not responding to pharmacotherapy, psychotherapy, and ECT. The mean (+/- SD) length of the current episode was 10.5 (+/- 7.4) years, the number of past treatment courses was 20.8 (+/- 8.4), the mean Hamilton Depression Rating Scale (HDRS) was 32.9 (+/- 5.1).
Results: Twelve months after initiation of DBS treatment 7 patients reached the response criterion (Responders, HDRS = 15.4 (+/- 2.8). The number of hedonic activities increased significantly in the responders only. Interestingly, ratings of anxiety measured with the Hamilton Anxiety Scale were reduced in both responders and non-responders, but more pronounced in the responders.
Conclusions: We demonstrate antidepressant and anti-anhedonic effects of DBS to NA in patients suffering from extremely TRD. In contrast to other DBS depression studies, there was a specific anti-anxiety effect. The presentation will discuss relevance of these results and others from DBS studies for the understanding of TRD.
Supported by limited funding of Medtronic Inc. for IIT

SYMPOSIUM
Gene Expression Across Human Brain Development and Schizophrenia
Thursday, May 20, 2010 12:30 PM - 2:30 PM
Location: Bayside BC - 4th Floor
Chair: Joel E. Kleinman

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13. Dysbindin-1 Transcripts and Isoforms are Differentially Affected in Schizophrenia

Konrad Talbot

University of Pennsylvania, Philadelphia, PA

Background: Dysbindin-1 is encoded by DTNBP1, a top candidate gene in schizophrenia (Sz). Its reference sequence transcripts encode the protein's major isoforms: dysbindin-1A, -1B, and -1C. Sz cases often display lower dysbindin-1 levels in the hippocampal formation (HF), but the causes and affected isoforms remain unknown.
Methods: We studied cultured lymphoblastoid cells from controls and postmortem brain tissue from schizophrenia cases and matched controls. We quantified DTNBP1 gene expression using qRT-PCR with primer pairs for the major transcripts. We quantified dysbindin-1 isoforms and TRIM32 using Western blotting with validated antibodies.

Results: Dysbindin-1 isoforms were differentially localized in cell nuclei and synaptosomes. In the latter, 1A and -1C were mainly associated with postsynaptic densities, while 1B was mainly associated with synaptic vesicles. Dysbindin-1 reductions were common in multiple brain areas in Sz: 1A in auditory cortices, 1B in the HF, and 1C in the HF and dorsolateral prefrontal cortex (DLPFC). Only levels of the 1B transcript were lower in lymphoblastoid cells carrying a DTNBP1 haplotype associated with Sz (Funke et al., 2004). With or without that haplotype, the DLPFC of Sz cases displayed reduced levels of 1C with normal levels of 1C transcripts. This reduction may result from posttranslational modifications promoting 1C degradation since the E3 ubiquitin ligase TRIM32 binds dysbindin-1, is postsynaptically located, and is inversely correlated with 1C in synaptosomes.
Conclusions: Studies on dysbindin-1 in Sz need to discriminate among its isoforms, especially since their differential distribution in neuronal nuclei and synapses appears to reflect different roles in transcription and synaptic transmission.
Supported by RO1 MH072880; P50 MH064045

14. Epigenetic Markings in Developing and Diseased Prefrontal Neurons

Schahram Akbarian

University of Massachusetts Medical School

Background: Histone modifications and DNA methylation, by shaping gene expression patterns and genome organization, are viewed as critical intermediates for numerous genetic and environmental factors exerting long-lasting influences on neuronal function in the human cerebral cortex. To date, however, comprehensive and genome-wide maps of neuronal epigenomes, and their developmental trajectories, do not exist.
Methods: Here, we provide first insights into neuronal epigenomes from the human PFC, by studying the genome-wide distribution of trimethyl histone H3K4 (H3K4me3)_ an epigenetic mark highly regulated at sites of actual or potential transcription_ in neuronal nuclei at various stages of normal postnatal development, and in a case-control cohort that includes subjects with schizophrenia.
Results: Massively parallel sequencing identified approximately 17,000-22,000 H3K4me3 enriched regions (peaks), with 59-69% located proximal to (within 2 kb) of the transcription start sites (TSS) of annotated genes.We provide (i) evidence for neuron-specific chromatin signatures and distinct individual epigenomes (ii) describe neurodevelopmental trajectories of histone methylation markings genome-wide,and (iii) explore potential alterations in schizophrenia and related disease.
Conclusions: Mapping entire epigenomes from defined cell populations of the human brain is feasible and likely to uncover novel molecular mechanisms governing normal and diseased neurodevelopment.
Supported by National Institutes of Health

15. Cellular Expression Profiling of Neurotransmitter Receptors in Human Brain

Andreas Jeromin

Banyan Biomarkers, Alachua, FL

Background: The Allen Brain Atlas is the first large scale atlas of gene expression in the mouse brain, using chromogenic in situ hybridization (cISH) of over 20,000 genes.
Methods: Subsequently, a platform automated high-throughput in-situ hybridization (ISH) in postmortem human brain has been established. Each tissue sample is first characterized for RNA integrity, presence of senile plaques, ice crystals and cortical region. Target mRNAs are detected by incubating tissue with custom-designed digoxigenin-labeled riboprobes, followed by signal amplification. Thionin-based Nissl staining is performed on a set of tissue sections from each sample to provide reference cytoarchitectural information for comparison with gene expression data. All ISH and Nissl data are then digitized using automated high-throughput microscopy.
Results: Initially, two cortical regions: visual and temporal cortex have been analyzed Approximately 1000 genes from various gene families are currently available in the dataset (http://humancortex.alleninstitute.org) and include cortical cell type markers (laminar, interneuron, glial, and vascular markers), gene families important to neural function (ion channels, G-protein-coupled receptors, transporters, synaptic proteins, membrane proteins, and numerous other disease-related genes.
Conclusions: I will report on differences in the expression and localization of neurotransmitter receptor between these two cortical regions in the human brain and compare them to expression in mouse brain. This comparison points towards possible cell-type specific differences in the expression of neurotransmitter receptors between human and mouse brain.

16. Genetic Regulation of Human Cortical Gene Expression Across the Lifespan

Barbara K. Lipska

NIMH, Bethesda, MD

Background: Understanding of genetic effects on expression obtained from genome-wide/transcriptome-wide studies is necessary for determining the underlying biology of associations with common diseases of the human brain. In this study, we focused on the molecular features of human prefrontal cortical development as they pertain to neurodevelopmental psychiatric disorders, such as autism and schizophrenia.
Methods: We assessed the effects of allelic variation, age, sex and race-related factors on transcript expression in ~270 non-psychiatric subjects throughout the lifespan, including the 2nd trimester of fetal life using two-color custom-spotted arrays with the Illumina Oligoset of 49,152 70-mer probes.
Results: Our results confirm marked changes in the expression of genes across the human lifespan, i.e., ~700 genes/probes show significant changes during fetal period (p<10-5), of which 64% increase expression with age, and ~3,800 genes/probes show significant changes from birth through young adulthood (p<10-5). Most importantly, our data indicate dramatic effects of genetic variability on human brain gene expression. We identified 14,125 significant genome-wide associations between genotype and expression (p values ranging from $5e^{-79}$ to $1e^{-08}$, at FDR 1.5%). Cis-acting SNPs, especially those in the gene and at a distance <100 Kb in 5' or 3' direction, showed the highest confidence as compared to trans-acting SNPs.
Conclusions: Our results emphasize the importance of establishing a database of human transcriptome across the human lifespan, including a potentially critical period of early brain development, and a database of polymorphisms affecting expression.

SYMPOSIUM

Neuropeptides and Interpersonal Psychopathology

Thursday, May 20, 2010 12:30 PM - 2:30 PM

Location: Maurepas - 3rd Floor

Chair: Larry J. Siever

Co-Chair: Jon-Kar Zubieta

17. Neural Mechanisms of Prosocial Neuropeptide Action in Human Brain: Challenge and Genetic Studies

Andreas S. Meyer-Lindenberg

Central Institute of Mental Health

Background: Neuropeptides are essential mediators of social behavior in mammals, including humans. Variations in the genes encoding the brain receptors for oxytocin (OXTR) and vasopressin (AVPR1A) have been linked to risk for autism, a heritable disorder with pronounced abnormalities in social recognition and function, and to social-behavioral phenotypes and temperament in healthy humans.
Methods: Here, we use imaging genetics, an approach to combine genetic assessment with multimodal neuroimaging to discover neural systems linked to genetic abnormalities or variation, to identify neural systems linked to neuropeptide receptor genetic variation, and challenge studies where healthy subjects receive neuropeptide or placebo in an fMRI paradiigm
Results: In AVPR1A, we found that differential activation of amygdala is observed in carriers of risk alleles for RS3 and RS1. Alleles in RS1 previously reported to be significantly over- and undertransmitted to autistic probands showed opposing effects on amygdala activation. Furthermore, we show functional difference in human brain between short and long repeat lengths that mirror findings recently obtained in a corresponding variant in voles. Challenge studies reveal a specific impact on regulatory interactions of prefrontal cortex. In OXTR, sex-specific effects on amygdala-hypothalamic-prefrontal circuits can be defined that mediate genetic effects on temperament such as reward dependence.Challenge studies show an impact on amygdala and related brainstem circuitry.
Conclusions: Our results indicate neural mechanisms mediating genetic risk for autism through an impact on amygdala signalling, and brain effects of acute neuropeptide stimulation, that and provide a rationale for exploring therapeutic strategies aimed at abnormal amygdala function in this disorder.
Supported by BMBF / DFG / NIH IRP

18. Dopamine-Opioid Interactions in Attachment Style and Impulsivity Traits

Jon-Kar Zubieta

University of Michigan

Background: Dopaminergic (DA) and opioid systems are critical modulators of brain regions and circuits implicated in motivated and attachment behavior and emotional regulation. These regions include the ventral striatum, pallidum, amygdala, insular cortex and cingulate and frontal cortices.
Methods: The concentration of DA D2/3 and μ-opioid receptors and the response of these systems to a standardized stressor was studied in healthy 22 males and 22 females with PET. Scans were obtained with [11C]raclopride and [11C]carfentanil and receptor availability (binding potential, BPND) quantified with Logan plots. A moderate level of pain maintained over 20 min was utilized as the stressor, matched in intensity between subjects.
Results: ANOVA showed the presence of significantly greater experimental stress-induced DA release in females, compared to males, in nigrostriatal and mesolimbic fields of the basal ganglia. In females, but not males, positive correlations were obtained between stress-induced DA release in the nucleus accumbens and measures of attachment anxiety and avoidance (r=.42 and r= .40, p<.05), respectively. For the μ-opioid system, significantly greater stress-induced release was observed in males, compared to females, in thalamus, nucleus accumbens and amygdala. Significant correlations (p<.05) were obtained in the male group between stress-induced μ-opioid system activation and impulsivity scores in the orbitofrontal cortex (r = .63), nucleus accumbens (r = .49), anterior thalamus (r = .61), and amygdala (r = .50).
Conclusions: These data show that DA and opioid neurotransmission are implicated in the regulation of personality characteristics related to motivated behavior (attachment styles and impulsivity) in humans, and sex differences in these phenomena.
Supported by R01 DA 016423

19. Opioids and Oxytocin: Genotypes and Phenotypes in BPD

Larry J. Siever[1], Colin A. Hodgkinson[2], Shauna Weinstein[1], Pei-Hong Shen[2], Antonia S. New[1], David Goldman[2]

[1]Mount Sinai School of Medicine, New York, NY, [2]NIAAA/NIH, Rockville, MD

Background: Neuropeptides play a mediating role for behaviors in the interpersonal domain including separation distress, affiliation, and attachment behaviors, all implicated in borderline personality disorder (BPD). Opioids have been associated with self-injurious behavior, capacity to self-soothe, and separation distress, while oxytocin has been associated with interpersonal affiliation and trust.
Methods: Delta opioid receptor (OPRD1), mu-opioid receptor (OPRM1) and oxytocin SNPs were analyzed in samples from 235 BPD patients, 131 patients with other personality disorders, 155 healthy controls in relation to diagnostic group membership, BPD traits, and trauma history.
Results: Three of 11 SNPs in the OPRD1 gene showed significant associations with identity disturbance and interaction with a history of trauma. 4 of 24 of the OPRM1 SNPs showed significant associations with affective lability with an interaction with history of trauma. One (rs#510769) withstood Bonferonni correction and was associated with reduced prefrontal activation in response to provocation on PET. SNP rs#877172 of four SNPs of OXT withstood correction and demonstrated a significant association with inappropriate, intense anger.
Conclusions: These data suggest that polymorphisms in the genotypes for oxytocin and for the opioid receptors may contribute to the interpersonal disturbance of BPD driven by identity and affective disturbance amplified by a history of trauma. These data in conjunction with other imaging and laboratory data from our and other centers generate models of opioid and oxytocin pathology in BPD.
Supported by Veterans Affairs VISN 3 Mental Illness Research, Education & Clinical Center; Mt Sinai GCRC - M01-RR-00071 National Center for Research Resources (NCRR)

20. Association between Endogenous Opioids and Childhood Neglect and Abuse

Barbara Stanley

Columbia University/NYSPI

Background: The neurobiological alteration associated with childhood neglect has received limited attention. The opioid system modulates responses to acute and chronic, stressful and noxious stimuli which induce subjective physical, emotional, or social pain and may be altered in individuals with histories of childhood neglect. The objective is to examine alteration of endogenous opioids in psychiatric patients with a history of childhood abuse and/neglect and to determine whether endogenous opioids mediate the relationship

between childhood trauma and non-suicidal self-injury (NSSI).
Methods: We compared cerebrospinal fluid (CSF) levels of endogenous opioids, 5 hydroxyindolacetic acid (5-HIAA) and homovanillic acid (HVA) in individuals with and without histories of childhood abuse or childhood neglect in a diagnostically-matched group of individuals. All patients were diagnosed with a Cluster B personality disorder (i.e. borderline, antisocial, narcissistic or histrionic) (N=29). Fourteen participants had a history of adulthood repeated non suicidal self-injurious behavior (NSSI) and 15 did not (no-NSSI).
Results: Childhood neglect but not physical and sexual abuse was related to significantly lower levels of CSF β-endorphin and met-enkephalin. CSF dynorphin, HVA and 5-HIAA levels did not differ. Furthermore, CSF β-endorphin and met-enkephalin levels are also lower in those with repetitive self injury.
Conclusions: Lower CSF β-endorphin and met-enkephalin, opioids acting upon receptors involved in mediating stress-induced and physical pain analgesia respectively, are implicated in childhood neglect and NSSI and may mediate the relationship between neglect history and NSSI.
Supported by NIH R01MH61017,R01MH62665, P20P20 AA015630

SYMPOSIUM
Recent Advances in fMRI-based Functional Connectivity Analysis in Affective Disorders
Thursday, May 20, 2010 12:30 PM - 2:30 PM
Location: Grand Ballroom ABC
Chair: J. Paul Hamilton*
Co-Chair: Amit Etkin

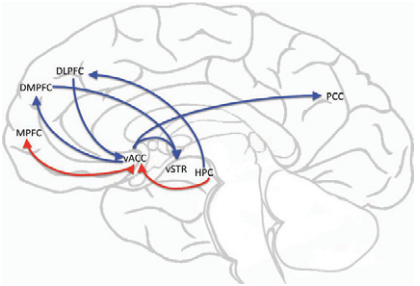
*Supported by NIH-F32MH079651

21. Investigating Neural Primacy in Major Depressive Disorder: Multivariate Granger Causality Analysis of Resting-State FMRI Time-Series Data

J. Paul Hamilton

Stanford University

Background. Major Depressive Disorder (MDD) has been conceptualized as a neural network-level disease. Applying analytic techniques that are capable of identifying aberrant directional relations among multiple neural ensembles is necessary for constructing a comprehensive neural theory of MDD.
Methods. We used multivariate Granger causality analysis — a technique that estimates the extent to which preceding neural activity in one or more seed regions predicts subsequent activity in target brain regions — to analyze blood-oxygen-level dependent (BOLD) data collected during rest in depressed and never-depressed persons.
Results. We found that activation in the hippocampus predicted subsequent increases in ventral anterior cingulate cortex (vACC) activity in depression, and that activity in medial prefrontal cortex and vACC were mutually reinforcing in MDD. Hippocampal and vACC activation in depressed participants predicted subsequent decreases in dorsal cortical activity.
Conclusions. This study shows that there is increased excitatory activity among limbic and paralimbic structures, as well as increased inhibition in activity of dorsal cortical structures, by limbic structures in depression; these aberrant patterns of effective connectivity implicate disturbances in the mesostriatal dopamine system in depression. These findings advance neural theory of depression by detailing specific patterns of limbic excitation in MDD, by making explicit the primary role of limbic inhibition of dorsal cortex in the cortico-limbic relation posited to underlie depression, and by presenting an integrated neurofunctional account of altered dopamine function in this disorder.



Supported by F32MH079651

22. Connectivity Analysis in Major Depressive Disorder Using Vector Autoregressive Models of Event-Related fMRI Data

Wesley K. Thompson

University of California, San Diego

Background: Neuroscientists have become increasingly interested in exploring dynamic relationships among brain regions. Such a relationship, when directed from one region toward another, is denoted by ``effective connectivity.'' An fMRI experimental paradigm which is well-suited for examination of effective connectivity is the slow event-related design. This design presents stimuli at sufficient temporal spacing for determining within-trial trajectories of BOLD activation. However, while several analytic methods for determining effective connectivity in fMRI studies have been devised, few are adapted to the characteristics of event-related designs, which include non-stationary BOLD responses and nesting of responses within trials and subjects.
Methods: We propose a model tailored for exploring effective connectivity of multiple brain regions in event-related fMRI designs - a semi-parametric adaptation of vector autoregressive (VAR) models, termed "stimulus-locked VAR" (SloVAR). Connectivity coefficients vary as a function of time relative to stimulus onset, are regularized via basis expansions, and vary randomly across subjects.
Results: We demonstrate the SloVAR model on a sample of clinically depressed and normal controls, showing that early but not late cortico-amygdala connectivity appears crucial to emotional control and early but not late cortico-cortico connectivity predicts depression severity in the depressed group, relationships that would have been missed in a more traditional VAR analysis.
Conclusions: SloVAR obtains flexible, data-driven estimates of effective connectivity and hence is useful for building connectivity models when prior information on dynamic regional relationships is sparse. Indices derived from the coefficient estimates can also be used to relate effective connectivity estimates to behavioral or clinical measures.
Supported by 5 K25 MH076981-02

23. Fronto-Cingulate Effective Connectivity in Major Depression: A Study with fMRI and Dynamic Causal Modeling

Ralf G.M. Schlösser

Psychiatry, University of Jena, Jena, Germany

Background: Functional imaging studies are indicating disrupted error monitoring and executive control in a fronto-cingulate network in major depression. However, univariate statistical analyses allow only for a limited assessment of directed neuronal interactions.
Methods: We used fMRI and dynamic causal modeling (DCM) of a fronto-cingulate network to examine 16 drug-free patients with major depression and 16 healthy controls performing the Stroop Color-Word Test.
Results: In both groups, a significant reciprocal interregional connectivity was

found in a cognitive control network including prefrontal cortex (PFC) and dorsal anterior cingulate cortex (ACC). With regard to intrinsic connections we detected a significant difference for dorsal to rostral ACC connectivity between depressive patients and controls in terms of higher connectivity in patients. Additionally, a task by group interaction was observed for the bilinear interaction signaling enhanced task-related input from the dorsal to rostral ACC in subjects with depression.
The correlation between interference scores and intrinsic connections from dorsal ACC to dorsolateral PFC (DLPFC) was significant for both groups together, but no significant group differences in correlations could be detected. Thus, the observed relationship between control functions of the dorsal ACC exerted over DLPFC and interference scores appears to be valid in both patients with depression and controls.
Conclusions: The present results could be related to the inability of patients to down-regulate rostral ACC activation as observed in previous univariate data analyses. The findings are consistent with current models of a differential involvement of the fronto-cingulate system in the pathophysiology of major depression.
Supported by BMBF, grants AQ4 FKZ01ZZ0405 and 01GW0740

24. Disrupted Amygdalar Subregion Functional Connectivity and Evidence for a Compensatory Network in Generalized Anxiety Disorder

Amit Etkin

Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA

Background: Studies in other anxiety disorders have implicated a role for the amygdala, but work in generalized anxiety disorder (GAD) has yielded conflicting results. The amygdala, however, is composed of distinct subregions that interact with dissociable brain networks, which have thus far been studied only in experimental animals. A functional connectivity approach at the subregional level in humans may therefore yield novel insights into GAD. Here, I will present data on the differential functional connectivity of two main subregions of the human amygdala and abnormalities in their connectivity in GAD.
Methods: Two cohorts of healthy subjects (N=17, N=31) and patients with GAD (N=16) were imaged during resting-state functional MRI. Subregional functional connectivity was examined using cytoarchitectonically-determined basolateral (BLA) and centromedial (CMA) regions of interest.
Results: Reproducible subregional differences in large-scale connectivity were identified in both cohorts of healthy subjects. The BLA was differentially connected with primary and higher order sensory and medial prefrontal cortices. The CMA was connected with the midbrain, thalamus and cerebellum. In patients with GAD, subregional connectivity patterns were significantly less distinct. Across subregions, patients had increased connectivity with a fronto-parietal "executive control" network and decreased connectivity with an insula and cingulate-based "salience" network.
Conclusions: Our findings provide new insights into the functional neuroanatomy of the human amygdala and converge with connectivity studies in experimental animals. In GAD, we find evidence for both an intra-amygdalar abnormality at a subregional level, as well as compensatory engagement of a fronto-parietal executive control network, consistent with cognitive theories of GAD.

SYMPOSIUM
Neurogenesis, Angiogenesis and Synaptogenesis Regulation
Thursday, May 20, 2010 12:30 PM - 2:30 PM
Location: Borgne - 3rd Floor
Chair: Maura Boldrini*
Co-Chair: Victoria Arango**

*Supported by PHS Grants MH40210, MH62185, MH64168, MH083862, American Foundation for Suicide Prevention.
**Supported by MH40210, MH83862, MH64168, MH62185

25. Vascular Remodeling Mechanisms in the Hippocampus

Samuel Sathyanesan

Yale University

Background: Recent appreciation of the neurovascular unit in brain function and homeostasis has suggested that a neuron-centric approach could limit our understanding of neuropsychiatric disorders. The induction of angiogenic factors and resultant effects on endothelial proliferation and increased vascular density has been demonstrated after electroconvulsive seizure (ECS). ECS-induced angiogenic factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF2) have been independently shown to elicit antidepressant effects in animal behavioral models. Taking into consideration these findings and the robust bidirectional relationship between cardiovascular disease and depression, we propose cerebral vasculature as a locus for pathology in depression.
Methods: Employing a combination of immunohistochemistry, gene expression, laser microdissection and immuno-insitu hybridization we investigated the regulation of angiogenesis in the rat hippocampus.
Results: Within this conceptual vascular framework we sought to understand angiogenic response in ECS and identified molecules and mechanisms that are involved in mediating vascular plasticity. Postmortem analysis of brain tissue from depressed patients showed destabilized cerebrovasculature and a decrease in expression of trophic factors. These results will be presented in the context of providing molecular insight into how angiogenic factor elevation can lead to formation of new vasculature in the hippocampus.
Conclusions: Our vascular hypothesis of depression could lead a new mechanistic direction of vascular research in psychiatric disease.

26. Differential Effect of Corticosterone on Neurogenesis and Angiogenesis

Anders Tingström, Joakim Ekstrand

Department of Clinical Sciences, Molecular Psychiatry Unit, Lund, Sweden

Background: The efficient antidepressant treatment ECT has recently been shown to increase hippocampal volume in depressed patients. This may be mediated via enhanced cell proliferation and enlargement of the neuropili. Stress and high levels of corticosterone (CORT) inhibit both neurogenesis and angiogenesis in the adult rat hippocampus. Similar mechanisms may lay behind the reduction in hippocampal volume that has been observed in depressed patients (where increased cortisol levels is a frequent finding). The aim of this study was to characterize the effect of electroconvulsive seizures (ECS), the animal model of ECT, on neuro- and angiogenesis in animals subjected to increased CORT levels.
Methods: Adult male Wistar rats, 200 g, three per cage, were used. The rats were treated with daily CORT (or vehicle) injections for seven days. During

the last 5 days they were either given one ECS or sham treatment. BrdU injections were given i.p. to label dividing cells. Hippocampal neurogenesis and angiogenesis was quantified using immunofluorescense microscopy.
Results: The stimulatory effect of ECS on angiogenesis was markedly reduced in CORT treated animals while the effect on neurogenesis remained.
Conclusions: Our data show that in the presence of high levels of stress hormones the angiogenic effect of ECS is blunted. Longer periods of ECS treatment may be required in order to overcome the CORT-induced inhibition of angiogenesis. Angiogenesis and neurogenesis share common growth factors, some of which have antidepressant properties. This line of research will aid in the understanding of the role of hippocampal cell growth / turnover for the effect of antidepressants.
Supported by Swedish Research Counsil, DNR 2006-5674

27. Antidepressants Increase Neural Progenitor Cells and Capillaries in the Human Dentate Gyrus

Maura Boldrini

Columbia University - New York State Psychiatric Institute

Background: Impaired adult neurogenesis is hypothesized in major depression (MDD), and antidepressants increase neurogenesis in the dentate gyrus (DG) of mammals and depressed patients. Neural progenitor cells (NPCs) replication occurs in neurogenic niches around small capillaries in the DG. Vascular endothelial growth factor regulates angiogenesis and neurogenesis, and it is increased by antidepressants in rodents. Newly generated capillaries, as well as NPCs, express the intermediate filament nestin. We sought to determine whether antidepressants increase nestin-immunoreactive (-IR) vessels and NPCs in the human DG.
Methods: We examined the relationship between the number and complexity of nestin-IR vessels and the number of nestin-IR NPCs in the DG of untreated MDDs, MDDs treated with selective serotonin reuptake inhibitors (SSRI) or tryciclics, and controls. After completion of psychological autopsy, toxicology and neuropathological examination, whole frozen hippocampi were fixed, sectioned and immunostained for nestin and Ki-67. Stereological cell counting and capillary measures were performed using StereoInvestigator (optical disector with fractionator) and Neurolucida.
Results: SSRIs increase the area of nestin-IR vessels (p=.001) and the number of NPCs (p=.039) in MDD subjects and the two are correlated (p=.00). SSRIs also increase the number of bifurcations of nestin-IR vessels in MDD (p=.049) and that correlates with the number of NPCs in the same subjects (p=.012). Age has a negative effect on capillary area (p=.050) and bifurcations (p=.049).
Conclusions: SSRIs have a stimulating effect on angiogenesis and neurogenesis in the human DG. Angiogenic regions can represent spatial targets for migrating neuroblasts, as well as a source for trophic support.
Supported by PHS Grants MH40210, MH62185, MH 64168, MH083862, American Foundation for Suicide Prevention

28. Roles of Bcl-2 Family Proteins and Mood Stabilizer-Induced Changes in Hippocampal Synapses in the Behavioral Regulation Related to Mood Disorders

Guang Chen

National Institute of Mental Health, National Institutes of Health

Background: Bcl-2 family proteins are the major modulator of apoptosis and resiliency. These proteins also mediate neuronal structure and functional plasticity. Although bipolar disorder (BPD) is traditionally conceptualized as a neurochemical illness, the human brain image and postmortem studies reveal brain regional morphological changes in BPD patients. Coherent with these findings, we found that mood stabilizers increased Bcl-2 expression in the brain, and enhanced known cellular function of Bcl-2, including neurite outgrowth, axonal regeneration, neuronal survival, and neurogenesis. Recently, we examined whether mood stabilizers alter the hippocampal synaptic proteome and whether the Bcl-2 effects are linked to BPD-related behavioral regulation.
Methods: Hippocampal synaptosomal proteomes were profiled after chronic lithium and valproate treatments using three biological repeats in each treatment group and a combination method of sucrose gradient ultra centrifugation, 2-D liquid chromatography, and tandem mass spectrometry. Immunoblot was used to confirm the proteomic findings. The Bcl-2 HET mice were phenotypied using a battery of behavioral tests tailed to detect mood disorder related changes.
Results: Proteomic experiments revealed several common lithium and valproate targets including a protein encoded by recently implicated bipolar risk gene, ANK3. Bcl-2 HET mice displayed increased sensitivity to behavioral deficits induced by uncontrollable and inescapable foot shocks and enhanced locomotor response to psychostimulants.
Conclusions: In addition to their neuronal morphological effects related to Bcl-2, mood stabilizers altered the synaptic profile. Given stress and psychostimulants can trigger mood episodes in euthymic BPD patients, the behavioral data suggest that Bcl-2 and its protein family are involved in the regulation of BPD vulnerability.
Supported by NIMH-IRP

SYMPOSIUM
Separation Distress in Non-Human Primates, Children, and Adults: Implications for Depression, Anxiety, Panic, and Grief

Thursday, May 20, 2010 12:30 PM - 2:30 PM
Location: Bayside A - 4th Floor
Chair: Peter J. Freed
Co-Chair: Stephen J. Suomi

29. GxE Interactions Influence Attachment in Non-Human Primates

Stephen J. Suomi

National Institutes of Health, Bethesda, MD

Background: In a variety of species, development of attachment to a caregiver is crucial for infant survival and partly mediated by the endogenous opioids. Functional mu-opioid receptor gene polymorphisms are present in humans (OPRM1 A118G) and rhesus macaques (OPRM1 C77G). We hypothesized that rhesus infants carrying a gain-of-function OPRM1 77G allele would experience increased reward during maternal contact and would, therefore, display increased measures of attachment.
Methods: We collected behavioral data from rhesus macaques (n = 97) during early infancy and at 6 months of age, across four cycles of maternal separation (4 days) and reunion (3 days). Animals were genotyped for the OPRM1 C77G polymorphism, and the effects of this allele on attachment-related behaviors were analyzed.
Results: Infants carrying the G allele exhibited higher levels of attachment behavior during early infancy. During prolonged periods of maternal separation, although infant macaques homozygous for the C allele exhibited decreases in their levels of distress vocalization with repeated separation, this response persisted in G allele carriers. The OPRM1 77G allele also affected social preference during reunion. C/G infants spent increasing amounts of time in social contact with their mothers as a function of repeated separation and were less likely to interact with other individuals in the social group, a pattern not observed among infants with the C/C genotype.
Conclusions: These findings suggest a role for OPRM1 variation in the expression of attachment behavior in human subjects, especially as a function of separation from the caregiver.

30. Gene and Physiological and Correlates of Social Behavior in Monkeys Experiencing Maternal Separation

Judy Cameron

Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA

Background: Social stress caused by maternal loss during early development can trigger anxious and depressive behavior in children and adults. Social support may modulate the development of this behavior, and as shown by this study the timing of maternal loss has an important impact on determining the outcome on behavior and brain development.
Methods: Infant monkeys were reared in small social groups and experienced separation from their mothers at four developmental times: 1 week, 1 month, 3 months and 6 months of age.
Results: Monkeys whose mothers were removed from the social group at 1 week exhibited fewer social behaviors and increased self-comforting behavior over development, whereas monkeys whose mothers were removed at 1 month exhibited increased seeking of social comfort. Changes in mRNA content in the amygdala tissue was also tested to identify neural systems that may contribute to the stress-induced behavioral changes. Guanylate Cyclase 1 alpha 3 (GUCYIA3) found in the right medial temporal lobe, showed differences in expression from the monkeys whose mothers were removed from the social group at 1 week compared to monkeys whose mothers remained in the social group. Also, differences in GUCY1A3 were apparent in the 1 week separated versus the 1 month separated infant monkeys.
Conclusions: This gene is positively correlated with social-comforting behavior, longer-term close social behavior, and negatively correlated with self-comforting behaviors.

31. The Neurobiology of Altered Socio-Emotional Behavior in Maternally Deprived Human Children

Nim Tottenham

UCLA, Los Angeles, CA

Background: Numerous non-human animal studies have shown that the amygdala and associated socio-emotional behaviors are particularly sensitive to maternal deprivation early in life (Kikusui & Mori, 2009; Plotsky et al., 2005; Sabatini, et al., 2007). Parental deprivation is very rare in human populations, and experimental control of timing is near impossible. Institutional rearing (e.g., orphanage care), which is sparse, unstable, and regimented, is unfortunately a naturally occurring example of poor caregiving in humans, one with a documented enddate (when infants are adopted by a stable family). Orphanage rearing, even in the best circumstances, is typically followed by adverse socio-emotional outcome (including increased internalizing problems and anxiety). The current talk focuses on the neurobiology associated with altered emotional development following poor caregiving.
Methods: A combination of neuroimaging (structural and functional magnetic resonance imaging), eye-tracking, and behavioral methods were used to examine the neuroaffective phenotypes in children adopted out of orphanage care.
Results: Relative to a comparison group who experienced typical care, children adopted from orphanage care showed structural and functional alterations of the amygdala and associated socio-emotional difficulties.
Conclusions: These findings are consistent with previous reports describing negative effects of prolonged maternal deprivation in behavior and neurobiology. These data suggest that changes in limbic circuitry may mediate the association between early caregiving and the long-term emotional profile in children who have experienced poor early caregiving experiences.

32. Acute Expression of Separation Distress in Adult Humans Alters Activity in Brain Regions Encoding Reward Processing and Separation Distress

Peter J. Freed

Columbia University, New York, NY

Background: The death of an attachment figure triggers intrusive thoughts of the deceased, sadness, and yearning for reunion. Recovery requires reduction of symptoms. We hypothesized that symptoms might correlate with a capacity to regulate attention toward reminders of the deceased, and activity in, and functional connectivity between, prefrontal regulatory regions and the amygdala.
Methods: Twenty recently bereaved subjects rated intrusive thoughts of the deceased versus a capacity to avoid thoughts (grief style). Reaction time was measured while subjects completed an Emotional Stroop (ES) task contrasting deceased-related with control words during functional magnetic resonance imaging (fMRI). Subjects subsequently visualized the death of the deceased and rated induced emotions.
Results: Subjects demonstrated attentional bias toward deceased-related words. Bias magnitude correlated with amygdala, insula, dorsolateral prefrontal cortex (DLPFC) activity. Amygdala activity predicted induced sadness intensity. A double dissociation between grief style and both prefrontal and amygdala subregion activity was found. Intrusiveness correlated with activation of ventral amygdala and rostral anterior cingulate (rACC); avoidance correlated with deactivation of dorsal amygdala and DLPFC. A double dissociation between regulatory region and task-dependent functional connectivity (FC) was found. High DLPFC-amygdala FC correlated with reduced atten- tional bias, while low rACC-amygdala FC predicted sadness intensity.
Conclusions: Results are consistent with a model in which activity in and functional connectivity between the amygdala and prefrontal regulatory regions indexes differences in mourners' regulation of attention and sadness during pangs of grief, and may be used to distinguish between clinically relevant differences in grief style.

SYMPOSIUM

CSTC Circuits in the Pathogenesis of ADHD

Thursday, May 20, 2010 12:30 PM - 2:30 PM

Location: Nottoway - 4th Floor

Chair: Bradley S. Peterson

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33. Prefrontal Circuits, Psychostimulants, and Default-Mode Processing in ADHD

Bradley S. Peterson[1,2]

[1]Department of Child Psychiatry, New York State Psychiatric Institute, New York, NY, [2]Columbia University, New York, NY

Background: The mechanisms by which psychostimulants improve attentional functioning in persons with ADHD are unclear.
Methods: Anatomical scans were acquired in 51 ADHD and 63 healthy control participants. Functional MRI scans were acquired twice in an additional 16 ADHD youth on and off stimulant medications and in 20 controls when performing a word-color Stroop task.
Results: Reduced local volumes of the inferolateral prefrontal cortex were detected in the ADHD group. Deficient activity of that same region was noted during performance of the Stroop task when not taking stimulant medication, and that activation increased when the same subjects were taking stimulant medication.

The more this region increased in activation in response to stimulant medication, the greater the suppression of default-mode activity in the ventromedial prefrontal cortex these youth were able to generate, and the greater was their reduction in ADHD symptom severity. Granger causality analyses indicated that functional connectivity between these regions also increased with stimulant administration.
Conclusion: Stimulants improve the functional activation of the inferolateral prefrontal cortex and its functional connectivity with the ventromedial prefrontal cortex. That improved connectivity seems to improve suppression of default-mode activity, which has been shown previously to correlate with mind-wandering during attentional tasks. Stimulants therefore may improve attention by improving functional interactions in these prefrontal circuits, which in turn reduces mind-wandering during attentional tasks.

34. Morphological Abnormalities of the Basal Ganglia and the Thalamus in ADHD

Iliyan Ivanov

Psychiatry, Mt Sinai School of Medicine, New York, NY

Background: Neuroimaging studies in humans have identified morphological and functional abnormalities in components of the cortico-striatal-thalamic networks such as the frontal and temporal cortices as well as the basal ganglia in individuals with ADHD; however, inconsistencies in the existing reports and lack of data on particular structures such as the thalamus have hampered advancement in the understanding of the role of the cortico-striatal-thalamic networks in the pathogenesis of ADHD.
Methods: Two groups of individuals with ADHD (N=47) and healthy controls (N=59) ages 8-18 underwent a structural MRI scan on 1.5-T scanner. Within the ADHD group 31 patients were receiving stimulant treatment at the time of the scan. A mixed analytic model with repeated measures was performed with SAS software to compare conventional volumes between groups; surface analyses p-values (threshold < 0.001) were color-coded at each voxel and displayed across the surface of the reference structures.
Results: No between groups differences were detected in the conventional volumes of the basal ganglia and the thalamus. Regional volumes of the caudate, putamen, globus palidus and the pulvinar were significantly larger in treated youth with ADHD compared to untreated counterparts. These areas closely overlapped with regions that exhibited significantly smaller local volumes in the ADHD vs. the control group.
Conclusions: This preliminary evidence demonstrates that i) youth with ADHD exhibit significantly smaller regional volumes than controls in the basal ganglia and the thalamus and that ii) stimulant treatment may help to attenuate these morphological differences in treated patients with ADHD.

35. Developmental Upregulation of Dopamine D2 Receptors in the Mouse Striatum Alters the Functioning of the Cortico-Striatal Cicuits

Christoph Kellendonk[1], Maxime Cazorla[1], Eleanor Simpson[1], Eric Kandel[1], Suzanne Haber[2], Sabine Krabbe[3], Jochen Roeper[3]

[1]Columbia University, New York, NY, [2]University of Rochester, Rochester, NY, [3]Goethe University Frankfurt, Frankfurt, Germany

Background: Alterations in the dopamine system during development have been implicated in the pathogenesis of attention deficit hyperactivity disorder (ADHD). Furthermore, brain imaging studies have identified anatomical locations in the cortico-striatal circuits that show structural abnormalities affecting the functional and anatomical connectivity of these circuits. One hypothesis is that in ADHD altered dopamine signaling during development may alter the connectivity of the cortico-striatal circuits. However, almost nothing is known about whether altered dopamine signaling during development really would affect the organization of these circuits.
Methods: We analyzed the behavior, physiology and anatomy of genetically modified mice, in which D2 receptors have been selectively up-regulated in the developing striatum.
Results: Excess of striatal D2 receptors during development results in behavioral deficits that are dependent on the prefrontal cortex. These impairments are associated with functional deficits in the meso-cortical dopamine system and structural alterations in the axonal projections from the prefrontal cortex to the striatum.
Conclusions: These findings demonstrate a causal relationship between developmental D2 receptor upregulation in the striatum and an altered organization of the cortico-striatal circuits in mice. We propose that similar as in the mouse model changes in dopamine signaling could affect the development of the cortico-striatal circuits in ADHD.

36. Tonic and Phasic Norepinephrine in Attention-Deficit/Hyperactivity Disorder: Insights from a Neurocomputational Model of the Stroop Task

Tiago V. Maia, Bradley Peterson

Columbia University, New York, NY

Background: Relative to healthy controls, patients with attention-deficit/hyperactivity disorder (ADHD) exhibit increased interference, decreased accuracy, slower reaction times (RTs), and increased intra-individual RT variability in the Stroop task. Other tasks produce similar findings. We hypothesized that noradrenergic dysfunction provides a unified account for these deficits.
Methods: We developed a computational model of the brain circuits involved in the Stroop task, including the effects of tonic and phasic norepinephrine on those circuits. We ran the model with normal levels of tonic and phasic norepinephrine to simulate healthy controls, and with low levels of tonic norepinephrine, phasic norepinephrine, or both to simulate patients with ADHD. We also ran the model with high tonic and low phasic norepinephrine because one theory proposes that ADHD involves this combination.
Results: The simulation with low phasic and normal tonic norepinephrine behaved like patients with ADHD, exhibiting increased interference, decreased accuracy, slower RTs, and increased intra-individual RT variability relative to the simulation of healthy controls. Low tonic norepinephrine combined with low phasic norepinephrine strengthened these effects. Low tonic norepinephrine alone also produced decreased accuracy, slower RTs, and increased intra-individual RT variability, but it did not produce increased interference. High tonic and low phasic norepinephrine produced decreased interference, decreased accuracy, faster RTs, and decreased intra-individual RT variability, which, with the exception of accuracy, are effects opposite to those found in patients with ADHD.
Conclusions: The deficits of patients with ADHD are consistent with low phasic norepinephrine, possibly but not necessarily accompanied by low tonic norepinephrine.
Supported by Klingenstein Third Generation Foundation

ORAL SESSION
Schizophrenia
Thursday, May 20, 2010 12:30 PM - 2:30 PM
Location: Southdown - 4th Floor
Chair: See Program Book

37. Genetically Determined Measures of Striatal D2 Signaling Predict Prefrontal Activity During Working Memory

Alessandro Bertolino[1], Paolo Taurisano[1], Nicola M. Pisciotta[2], Giuseppe Blasi[1], Leonardo Fazio[1], Raffaella Romano[1], Barbara Gelao[1], Luciana Lobianco[1], Madia Lozupone[1], Annabella Di Giorgio[1], Grazia Caforio[1], Fabio Sambataro[3], Artor Niccoli-Asabella[2], Audrey Papp[4], Gianluca Ursini[1], Lorenzo Sinibaldi[5], Teresa Popolizio[6], Wolfgang Sadee[4], Giuseppe Rubini[2]

[1]Department of Neurology and Psychiatry, University of Bari, Bari, Italy, [2]Department of Internal Medicine and Public Medicine, University of Bari, Bari, Italy, [3]Clinical Brain Disorders Branch, NIMH-NIH, Bethesda, MD, [4]Department of Pharmacology, Ohio State University, Columbus, OH, [5]Mendel Institute, IRCCS - Casa Sollievo della Sofferenza, Rome, Italy, [6]Department of Radiology, IRCCS - Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy

Background: Variation of the D2 receptor gene (*DRD2*) has been associated with schizophrenia and with working memory deficits. However, the effect of functional genetic variation of *DRD2* on striatal dopamine signaling and on its relationship with prefrontal activity during working memory is not known.
Methods: Thirty-seven healthy subjects were genotyped for rs1076560 (G>T), a functional intronic SNP associated with relative expression of the two D2 receptor isoforms, D2S (mainly pre-synaptic) and D2L (mainly post-synaptic). Subjects underwent SPECT with [^{123}I]IBZM (binding primarily to post-synaptic D2 receptors) and with [^{123}I]FP-CIT (binding to pre-synaptic dopamine transporters, whose activity and density is also regulated by pre-synaptic D2 receptors), as well as BOLD fMRI during N-Back working memory. Alla data were analyzed with random effects analyses in SPM5 (all $p<0.05$, corrected).
Results: Subjects carrying the T allele (previously associated with reduced D2S expression) had striatal reductions of [^{123}I]IBZM and of [^{123}I]FP-CIT binding. *DRD2* genotype also differentially predicted the correlation between striatal dopamine D2 signaling (as identified with factor analysis of the two radiotracers) and activity of the prefrontal cortex during working memory as measured with BOLD fMRI, which was positive in GG subjects and negative in GT.
Conclusions: Our results demonstrate that rs1076560 predicts striatal binding of the two radiotracers to dopamine transporters and D2 receptors as well as correlation between striatal D2 signaling with prefrontal cortex activity during working memory. A plausible mechanism associated with these effects is D2-mediated modulation of striatal outputs to prefrontal activity during working memory within the cortico-striatal-thalamic-cortical pathway.

38. Static and Dynamic Cognitive Deficits in Childhood Precede Adult Schizophrenia: A 30-Year Study

Abraham Reichenberg[1], Avshalom Caspi[2,3], HonaLee Harrington[3], Renate Houts[3], Richard S. Keefe[3], Robin M. Murray[1], Richie Poulton[4], Terrie E. Moffitt[2,3]

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Background: Premorbid cognitive deficits in schizophrenia are well documented, and have been interpreted as supporting a neurodevelopmental etiological model. We investigated 3 unresolved questions about premorbid cognitive deficits: (a) What is their developmental course? (b) Do all premorbid cognitive deficits follow the same course? (c) Are premorbid cognitive deficits specific to schizophrenia or shared by other psychiatric disorders?
Methods: Participants were members of a representative 1972-1973 birth cohort of 1,037 males and females in Dunedin, New Zealand, who were followed up to age 32 with 96% retention. We compared the cognitive development of three groups of children: those who developed schizophrenia, recurrent depression, and healthy controls.
Results: Children who developed adult schizophrenia exhibited developmental deficits (i.e., static cognitive impairments that emerge early and remain stable) on tests indexing verbal and visual knowledge acquisition, reasoning and conceptualization. In addition, these children exhibited developmental lags (i.e., growth that is slower relative to healthy controls) on tests indexing processing speed, attention, visual-spatial problem-solving ability and working memory. These two premorbid cognitive patterns were not observed in children who later developed recurrent depression.
Conclusions: These findings suggest that the origins of schizophrenia include two interrelated developmental processes evident from childhood to early adolescence. Future schizophrenia cases enter primary school struggling with verbal reasoning and, as they get older, they lag further and further behind their peers in working memory, attention and processing speed.
Supported by MRCG0100527, R01MH45070, R01MH49414, R01MH077874, R01AG032282, R01MH066105

39. Genetic Control Over the Default Mode Network

David C. Glahn[1], A. M. Winkler[1], P. Kochunov[2], L. Almasy[3], R. Duggirala[3], M. A. Carless[3], J. C. Curran[3], R. L. Olvera[4], A. R. Laird[2], S. M. Smith[5], C. F. Beckmann[5], P. T. Fox[2], J. Blangero[3]

[1]Psychiatry, Institute of Living/ Yale University, Hartford, CT, [2]Research Imaging Institute, University of Texas Health Science Center San Antonio, San Antonio, TX, [3]Genetics, Southwest Foundation for Biomedical Research, San Antonio, TX, [4]Psychiatry, University of Texas Health Science Center San Antonio, San Antonio, TX, [5]FMRIB, Oxford University, Oxford, United Kingdom

Background: The default-mode network, a coherent resting-state brain network, is thought to characterize basal neural activity. Aberrant default-mode connectivity has been reported in a host of psychiatric illnesses and in persons at genetic risk for such illnesses. While the neurophysiologic mechanisms that regulate default-mode connectivity are unclear, there is growing evidence that genetic factors play a role. Here, we estimate the importance of genetic effects on the default-mode network.

Methods: 333 individuals from 29 randomly selected extended pedigrees completed 7-min resting-state scans. Images were analyzed with FSL software and statistical genetic analyses were estimated with SOLAR.
Results: Heritability for default-mode functional connectivity was 0.424±0.17 (p=0.0046). Although neuroanatomic variation in this network was also heritable, the genetic factors that influence default-mode functional connectivity and gray-matter density are distinct, suggesting that unique genes influence the structure and function of the network. In contrast, significant genetic correlations between regions within the network suggest that the same genetic factors contribute to variation in functional connectivity throughout the default-mode.
Conclusions: Default-mode functional connectivity is influenced by genetic factors that cannot be attributed to anatomic variation or to a single region within the network. By establishing the heritability of default-mode functional connectivity, this experiment provides the obligatory evidence required before these measures can be considered as endophenotypes for psychiatric or neurological illnesses or to identify genes influencing intrinsic brain function.
Supported by MH0708143 (PI: DC Glahn), MH078111 (PI: J Blangero), MH083824 (PI: DC Glahn)

40. A Longitudinal Imaging-Genetics Study of Catechol-O-Methyltransferase Val158Met Genotype and Cortical Maturation in Youth with Childhood-Onset Psychosis, Their Non-Psychotic Siblings and Typically Developing Controls

Armin Raznahan, Yohan Lee, Dede Greenstein, Ajene Addington, Robert Long, Liv Clasen, Jay Giedd, Judith Rapoport, Nitin Gogtay

Child Psychiatry Branch, NIMH, NIH, Bethesda, MD

Background: Val158Met genotype modulates phenotypes important to schizophrenia (SCZ) neurobiology such as dopamine (DA) signaling (lower synaptic DA in Val vs Met), and pre-frontal cortical (PFC) structure/function. In adults with SCZ, and their non-psychotic siblings (NPS), deficits in PFC grey matter volume and function are greater with increasing Val dosage. In typically developing (TD) adults however, Val dosage has been less consistently linked to performance PFC structure and function. We hypothesised that these phenomena reflect differential influences of Val dosage on adolescent PFC maturation in SCZ and SIBs as compared to TDs.
Methods: We related Val allele "dosage" to cortical thickness (CT) trajectories between ages 9 and 22 years in 1111 longitudinally gathered structural brain MRI scans from 255 TD individuals, 87 individuals with severe childhood-onset SCZ (COS), and 89 of their NPSs.
Results: In bilateral temporal and dorsolateral-prefrontal cortices, the rate of CT loss across adolescence increased with increasing Val dosage in COS and NPS groups, whereas in the same areas normative cortical thinning in TDs was attenuated with increasing Val dosage. Further significant genotype-by-group differences in CT change were also seen between TD and COS groups in bilateral cingulate cortices.
Conclusions: Val-induced reductions of synaptic DA availability may exacerbate background abnormalities of cortical DA signaling shared by COS and SIBs, to amplify PFC grey matter deficits. Conversely, relatively intact DA systems in TDs may protect against these neurochemical and neurodevelopment consequences, resulting in increased Val dosage having the opposite effect of slowing normative cortical thinning.
Supported by NIMH Intramural, UK MRC

41. Metabotropic Glutamate Receptor and Endocannabinoid Signaling in the Prefrontal Cortex in Schizophrenia

David Volk[1], Stephen Eggan[1], David Lewis[2]

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Background: Cannabis use exacerbates prefrontal cortex (PFC)-related cognitive deficits in individuals with schizophrenia. This effect may reflect the aggravation of pre-existing deficits in GABA signaling because cannabis activates the cannabinoid 1 receptor (CB1R), which suppresses GABA release. Prefrontal CB1R mRNA and protein levels are lower in schizophrenia; however, the status of endogenous agonists for CB1R, such as 2-arachidonoylglycerol (2-AG), is unclear. Although 2-AG cannot be directly assessed in postmortem human brain tissue, its status can be inferred through measures of diacylglycerol lipase (DAGL) and monoglyceride lipase (MGL), which synthesize and degrade 2-AG, respectively, and group I metabotropic glutamate receptors, such as mGluR1α, which stimulate 2-AG synthesis.
Methods: We used quantitative PCR to measure mRNA levels for DAGL, MGL, mGluR1α, and other markers of the endocannabinoid system in PFC area 9 from 42 schizophrenia subjects and normal comparison subjects. We conducted similar studies in monkeys chronically exposed to haloperidol, olanzapine, or placebo.
Results: Schizophrenia subjects had higher mRNA levels for mGluR1α and lower mRNA levels for regulator of G protein signaling 4 (RGS4), which reduces the duration of signaling from mGluR1α. Furthermore, mGluR1α and RGS4 mRNA levels were not altered in antipsychotic-exposed monkeys. In contrast, no differences between subject groups were found in mRNA levels for other endocannabinoid regulators, including DAGL and MGL.
Conclusions: Higher signaling capacity through mGluR1α receptors may have diverse effects on neuronal communication in the PFC in schizophrenia, including increased 2-AG signaling which may contribute to impaired GABA neurotransmission and to cognitive deficits in schizophrenia.
Supported by NIH grants MH-084018 (Dr. Volk) and MH-043784, MH-084053 and a NARSAD Distinguished Investigator Award (Dr. Lewis)

42. Convergent Neuroimaging and Neuropsychological Studies of Progressive Decline in Cognitive Performance and Grey Matter Loss in Schizophrenia Following HSV1 Exposure

Konasale M. Prasad

Western Psychiatric Institute and Clinic

Background: An association between cognitive impairments and smaller prefrontal cortex (PFC) in schizophrenia (SZ) and exposure to herpes simplex virus, subtype 1 (HSV1) - a neurotropic virus is reported in the absence of encephalitis. We examined the longitudinal trajectory of executive functions and grey matter (GM) volume over 1-year among first-episode SZ subjects antipsychotic-naïve at baseline (n=44) and healthy subjects (HS; n=80).
Methods: Subjects were administered the Wisconsin Card Sorting Test at baseline, 6-months and 1-year. We examined perseverative errors, categories completed and a composite of executive functions using binomial random mixed effects growth models by including age, gender and socioeconomic status as covariates. Longitudinal GM changes over 1-year were examined using deformation fields analysis. Whole-brain false discovery rate-corrected results are presented.
Results: *WCST Scores:* Seropositive SZ scored lower on composite executive functions (p=0.0002), committed same number of errors (p=0.07), and completed fewer categories at 1-year compared to baseline (p<0.00001). Seronegative SZ

subjects' and HS did not change at 1-year. *Longitudinal Imaging:* SZ subjects but not HS showed GM loss in the posterior cingulate gyri (PCG) (left, T=11.43, FDR_p=0.002; right, T=8.49, FDR_p=0.005) at 1-year compared to baseline. Within SZ, seropositive SZ but not seronegative SZ and HS showed greater GM loss in the left PCG (T=13.77, FDR_p=0.034; 1.6 cc reduciton) and a trend for the right PCG (T=9.93, FDR_p=0.07; 0.66 cc reduction).
Conclusions: These convergent results suggest that longitudinal impairments in executive functions may partly be mediated through PCG GM loss in seropositive SZ subjects.
Supported by SMRI, MH72995

43. Why Transition to Psychosis is not the Whole Story - Neurocognitive Markers of Transition and Poor Functional Outcome Seven to 14 Years after Identification as Ultra-High Risk at the PACE Clinic

Stephen J. Wood[1], Ashleigh Lin[1], Alison R. Yung[2], Warrick J. Brewer[2], Barnaby Nelson[2], Christos Pantelis[1]

[1]Melbourne Neuropsychiatry Centre, University of Melbourne, Parkville, Australia, [2]Orygen Youth Health Research Centre, University of Melbourne, Parkville, Australia

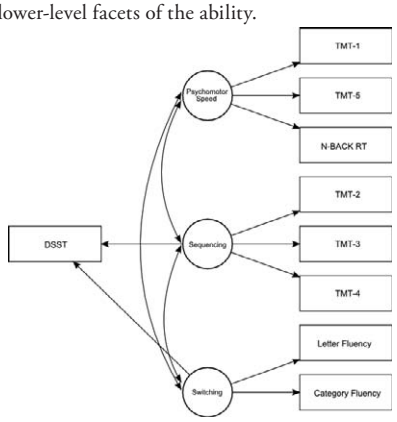
Background: The progression from ultra-high risk (UHR) to chronic psychosis remains unclear. Early predictors may help to better target intervention, although it is still unknown whether neurocognitive indicators when at risk can be used to predict transition to psychosis.
Methods: Transition data was collected from the first 198 individuals who were seen at PACE. Psychopathological, neuropsychological and functional outcome data was collected on 120 of these individuals. Using Cox regression survival analysis (for transition to psychosis) and logistic regression modelling (for functional outcome), we identified neurocognitive markers at baseline that predicted the transition to psychosis and poor functional outcome.
Results: Only lower visual memory scores at baseline were significantly associated with transition (p=0.001). The data, however, showed a number of individuals with very poor functional outcome, some of whom had never transitioned to psychosis. This group was defined by poor quality of life, low GAF, and high negative symptoms, and showed significantly worse baseline neurocognitive function across verbal and visual memory domains. When neurocognitive variables were modelled, the best model for predicting poor functional outcome included poorer verbal (p=0.004) and visual memory (p=0.02) and slower psychomotor speed (p=0.17).
Conclusions: Many individuals identified as UHR may not transition to psychosis, but still experience poor functional outcome and low quality of life. Poor neurocognitive performance when at UHR is more indicative of poor functional outcome than transition to acute psychosis. Using transition to psychosis as the only outcome measure in UHR research may be misleading.
Supported by NHMRC Australia

44. The Multidimensional Structure of Processing Speed in Healthy Individuals and Schizophrenia Patients

Emma E. M. Knowles[1], Mark Weiser[2], Michael Davidson[2], Anthony S. David[1], Avi Reichenberg[1]

[1]Psychological Medicine, Institute of Psychiatry, London, United Kingdom, [2]Psychiatric Division, Sheba Medical Centre, Ramat-Gan, Israel

Background: Recent research has identified processing-speed inefficiency, as measured by coding tasks, as the largest cognitive impairment in schizophrenia. However it is unclear to what degree processing speed is a multidimensional, as opposed to a unitary, construct; or how the structure of this construct differs between control and schizophrenia groups. In answering these questions this paper will provide further insight into the processing-speed impairment in schizophrenia.
Methods: 272 controls and 123 schizophrenia cases completed a set of putative measures of processing speed. We implemented confirmatory factor and structural equation modelling analyses (Miyake et al, 2000) to elucidate the latent structure of processing speed. Next, we tested the degree to which the structural and relational portions of the processing speed model was equal across groups.
Results: The best-fitting model revealed that processing-speed is a multidimensional hierarchical construct consisting of three lower-level factors measuring: 'Psychomotor Speed', 'Sequencing' and 'Switching'; with coding-task performance fitting in the model as a higher-level process affected directly by the 'Sequencing' and Switching' factors and indirectly by 'Psychomotor Speed'. The structure of the model was similar across groups but the strengths of the relationships within the models differed significantly (p<0.05).
Conclusions: Processing speed is similarly characterised in control and schizophrenia groups as a multidimensional construct wherein successful coding-task performance reflects a higher level-process, which is reliant on the co-ordination of multiple processing-speed factors. According to this model the overall processing-speed impairment in schizophrenia is underlain by impairment in lower-level facets of the ability.



Supported by R01MH066105

WORKSHOP
Ask the Editors:
A Workshop on Publishing in Psychiatry
Thursday, May 20, 2010 12:30 PM - 2:30 PM
Location: Oak Alley - 4th Floor

45. A Workshop on Publishing in Psychiatry

The purpose of this workshop is to provide attendees with an introduction to the "behind the scenes" processes that influence the decision to accept or reject a paper for publication. The workshop presenters include the editors of the American Journal of Psychiatry, Archives of General Psychiatry, Biological Psychiatry, and Neuropsychopharmacology. Each editor will briefly introduce their journal. These introductions will be followed by an open discussion that will cover current challenges and controversies in psychiatric publishing.

SYMPOSIUM
Imaging the Mechanisms of Genetic Liability to Bipolar Disorder
Thursday, May 20, 2010 3:00 PM - 5:00 PM
Location: Bayside BC - 4th Floor
Chair: Andrew M. McIntosh*
Co-Chair: Melissa DelBello

*Supported by The Health Foundation

46. Spatial Working Memory Related Brain Activation in Individuals with Bipolar Disorder and their Unaffected Siblings

David C. Glahn[1,2], Jennifer Barrett[2], Lauren Lombardo[2], Sarah Galvin[2]

[1]Department of Psychiatry, Yale University, New Haven, CT, [2]Olin Neuropsychiatry Research Center, Hartford, CT

Background: Individuals with bipolar affective disorder have working memory impairments even during periods of symptom remission. Reports that unaffected siblings of bipolar probands also have working memory deficits suggest that this cognitive domain may be sensitive to genetic liability for the illness. Despite evidence that working memory impairment may be a locus of dysfunction in bipolar disorder, the neural correlates of this imperilment is unclear.
Methods: In the present experiment, 20 sibling pairs discordant for bipolar disorder and 20 demographically matched comparison subjects performed a spatial delayed response task previously associated with risk for schizophrenia.
Results: Behavioral performance did not differ between groups. Compared to a sensory-motor control condition, all subjects activated a large-scale, spatially distinct network of brain regions that subserve working memory, including the dorsolateral prefrontal cortex (DLPFC), the superior and inferior parietal lobules and the anterior cingulate cortex. While patients with bipolar disorder engaged the DLPFC region less than healthy subjects, unaffected siblings did not differ from comparison subjects. Although all patients were remitted at the time of assessment, half previously experienced psychotic symptoms. Bipolar patients with history of psychosis had significantly less prefrontal and parietal activity than comparison subjects. Siblings of psychotic bipolar patients engaged the DLPFC and cingulate regions more than comparison subjects. In contrast, bipolar patients without history of psychosis and their siblings did not differ from comparison subjects in any region.
Conclusions: These data suggest that aberrant prefrontal and parietal activity may be sensitive to risk for psychotic bipolar disorder.
Supported by R01MH080912

47. Structural and Functional Brain Abnormalities in People at High Risk of Bipolar Disorder for Familial Reasons

Andrew M. McIntosh

University of Edinburgh

Background: Structural and fucntional abnormalities have been reported in people with bipolar disorder. The paucity of investigations in high risk groups means that there is uncertainty regarding the timing of these changes and their relationship to genetic liability.
Methods: One hundred and thirty subjects at high familial risk of bipolar disorder and 80 controls aged 16-25 were recruited and scanned prospectively using structural T1 and DTI-weighted imaging and a constrained verbal fluency fMRI paradigm.
Results: Subjects at high risk of bipolar disorder showed significant abnormalities in white matter structure, integrity and in brain function. No differences were found in grey matter density. These findings were related to risk alleles in SNPs previously associated with bipolar disorder.
Conclusions: Genetic vulnerability to Bipolar disorder is associated with white matter and functional deficits, but not to pre-existing deficits in grey matter density or volume. These must emerge later in life to explain the deficits found both in patients and older unaffected relatives.
Supported by The Health Foundation

48. Neurofunctional Brain Abnormalities in Adolescents At-Risk for Bipolar Disorder

Melissa DelBello, Caleb Adler, James Eliassen, Neil Mills, Stephen Strakowski

University of Cincinnati, Cincinnati, OH

Background: Recent findings suggest that adolescents with bipolar disorder exhibit structural and functional abnormalities in prefrontal and amygdala brain regions. We investigated whether these abnormalities are present prior to the onset of bipolar disorder in order to determine whether they may be useful predictors of illness.
Methods: Thirty-five adolescents (ages 10-20 years) with a bipolar parent and fifteen demographically-matched healthy comparison subjects without any first- or second-degree relatives with a mood disorder underwent functional MRI while performing a Continuous Performance Test with Emotional and Neutral Distracters (CPT-END). Ten of the at-risk adolescents were diagnosed with attention deficit hyperactivity disorder. Functional images were analyzed using Analysis of Functional Images (AFNI) and included motion correction, spatial smoothing, normalization and random effects analysis of activation data.
Results: At-risk and healthy adolescents exhibited differences in right Brodmann area 11-amygdala and right Brodmann area 47-amygdala connectivity. Specifically, activation in right BA 11-amygdala and right BA 47-amygdala was correlated in healthy adolescents (R^2=0.5 and 0.4, respectively) but not in at-risk adolescents with (R^2=0.1 and 0.2, respectively) or without (R^2=0.001, and 0.09, respectively) ADHD.
Conclusions: Our preliminary findings indicate that adolescents at risk for developing bipolar disorder exhibit alteration in ventral lateral prefrontal-amygdala coupling prior to illness onset and independent of ADHD, suggesting that these abnormalities may serve as predictors of incipient mood episodes.
Supported by P50MH077138

49. The Functional Consequences of Risk Genes for Bipolar Disorder on Neural Function

Sophia Frangou

Section of Neurobiology of Psychosis, Institute of Psychiatry, London, United Kingdom

Background: Current research efforts are focused on delineating the relationship between risk genes for Bipolar Disorder (BD) and neural systems or cognitive domains. We report our findings on the relationship between cognition and brain function in relation to three genes of interest, namely ANK3, CACNA1C and COMT.
Methods: Remitted patients with BD (n=47), their first degree relatives (n=75) and healthy controls(n=51) from the Vulnerability Indicators for Bipolar Disorders Study (VIBES) were genotyped and assessed in terms of cognition (using a broad cognitive battery) and emotional processing using facial affect discrimination as a probe during functional magnetic resonance imaging data acquisition.
Results: The three genotypes showed relatively specific associations (a) the ANK3 risk T allele was associated with decreased perceptual sensitivity and increased errors in a task of sustained attention regardless of diagnosis; this was more pronounced in BD patients (b) For the CACNA1C gene we found

a significant diagnosis by genotype interaction with BD patients homozygous for the risk allele having reduced prefrontal activation compared to the other groups during fearful affect processing (c) A significant genotype by diagnosis interaction was observed for the COMT gene with the Met158 allele being associated with greater activation in ventrolateral prefrontal cortex in patients during sad facial affect discrimination.
Conclusions: Our results suggest that key genes conferring increased risk for BD have a differential effect on cognition and emotional processing.

SYMPOSIUM

Comorbidity Between Alcohol, Nicotine and Drug Dependence: Origins, Effects and Treatment

Thursday, May 20, 2010 3:00 PM - 5:00 PM
Location: Nottoway - 4th Floor
Chair: Mary-Anne Enoch*

*Supported by NIAAA, NIH

50. Childhood Trauma and Variation in GABAergic and Serotonergic Genes Predict Alcohol, Heroin and Cocaine Dependence

Mary-Anne Enoch[1], Colin A. Hodgkinson[1], Elena Gorodetsky[2], Qiaoping Yuan[1], David Goldman[1], Alec Roy[3]

[1]LNG, NIAAA/NIH, Bethesda, MD, [2]NIMH/NIH, Bethesda, MD, [3]DVA, NJ VA Healthcare System, East Orange, NJ

Background: Environmental stressors and genetic factors influence risk for addiction. The GABRA2 gene and serotonin (5-HT) variation have been implicated in alcohol and drug dependence. The 5-HT transporter and 5-HT3 receptors respectively regulate the availability and fast transmission of synaptic 5-HT. We hypothesized that GABAergic and serotonergic genetic variation, childhood trauma and their interaction might influence risk for addiction.
Methods: African American men were recruited for this study: 577 treatment-seeking patients with lifetime DSM-IV single and comorbid diagnoses of alcohol, cocaine and heroin dependence and 255 controls. The childhood trauma questionnaire was administered. GABRA2 haplotype-tagging SNPs, a functional 5-HT3 (HTR3B) receptor polymorphism (Y129S) and the functional 5-HT transporter triallelic polymorphism HTTLPR were genotyped.
Results: Exposure to childhood trauma predicted alcohol, heroin and cocaine dependence ($p < 0.0001$). One GABRA2 haplotype predicted heroin dependence; another conferred resilience to addiction after exposure to severe childhood trauma. An independent GABRA2 SNP predicted heroin dependence and interacted with childhood trauma to influence cocaine addiction. The low activity HTTLPR variant (OR=2.5) and the gain-of-function HTR3B variant (OR=1.7) were significantly associated with alcohol and drug dependence. These two variants that act together to increase synaptic availability of, and receptor response to, 5-HT had an additive effect on alcohol and drug dependence (OR=6.0).
Conclusions: Our study sheds some light on the complex genetic-environmental influences on addiction. We have shown that childhood trauma, GABRA2 variation and their interaction play a role in risk-resilience. Moreover, the HTTLPR and HTR3B functional variants act synergistically to increase addiction vulnerability.
Supported by NIAAA

51. Association of Common Genetic Variants with Structural and Functional Brain Alterations in Alcohol and Nicotine Dependent Individuals

Vibhuti Srivastava[1], L. Elliot Hong[2], Beata Buzas[1], Reza Momenan[1], Colin A. Hodgkinson[1], Mary-Anne Enoch[1], Daniel W. Hommer[1], Elliot A. Stein[3], David Goldman[1]

[1]NIAAA, NIH, Rockville, MD, [2]Maryland Psychiatric Research Center, Department of Psychiatry, , University of Maryland School of Medicine, , Baltimore, MD, [3]NIDA, NIH, Baltimore, MD

Background: Structural and functional brain alterations are observed in alcohol and nicotine dependent individuals pointing towards interactions between genes and drug exposures. We investigated the involvement of a functional variant of Superoxide dismutase 2 (SOD2), a gene implicated in oxidative stress, on gray matter shrinkage in alcohol dependent patients and the role of nicotinic acetylcholine receptor (nAChR) genes CHRNA5 and CHRNA3 SNPs which include at least one functional polymorphism modifying risk of nicotine dependence, on the dorsal anterior cingulate (dACC) - ventral striatum/extended amygdala functional circuit of nicotine-dependent individuals.
Methods: Brain volumes of 76 inpatient treatment-seeking alcoholics were measured with a 1.5T MRI. Two SOD2 tag SNPs including the functional rs4680 (Ala16Val) were genotyped. Three SNPs, functional rs16969968-Asp398Asn (CHRNA5) and, rs1051730 and rs578776 (CHRNA3) were genotyped in separate 311 non-alcoholics whose smoking status was ascertained. Resting state fMRI was obtained in 191 of these subjects and dACC was manually isolated.
Results: The homozygous SOD2 Ala16 diplotype was associated with gray matter shrinkage ($p=0.005$) in alcoholics. The risk/protective effect was dependent on alcohol exposure but only in alcoholics with lower levels of lifetime alcohol consumption ($p=0.03$). All three nAChR SNPs significantly differentiated smokers from nonsmokers. The CHRNA5 rs16969968 Asn398 risk allele was significantly associated with reduced functional connectivity in the dACC circuit that in itself predicted increased severity of nicotine addiction.
Conclusions: Our study has identified the association of functional genetic variations with brain volume and circuit connectivity in the two most common addictions. Identification of such genetic effects may provide prospective targets for novel pharmacological interventions.
Supported by NIH Intramural grant; NIH grants MH70644, 79172, 49826, 77852, 68580, and N01-DA-5-9909; University of Maryland General Clinical Research Center grant # M01-RR16500;Maryland Cigarette Restitution Fund Program – Other Tobacco-Related Diseases Resear

52. Neuroimaging Effects of Comorbid Alcohol and Nicotine Dependence: Implications for Treatment

Dieter J. Meyerhoff, Timothy C. Durazzo

UC San Francisco and VA Medical Center, San Francisco, CA

Background: The adverse effects of alcohol use disorders on brain biology and cognition and their changes during sustained abstinence are well documented. The brain effects of chronic smoking among alcoholics have rarely been considered. We postulate chronic cigarette smoking among alcoholics modulates brain injury, cognition and recovery during abstinence from alcohol.
Methods: We compared smoking to non-smoking alcoholics at entry into treatment and at 5 weeks and 8 months of abstinence on quantitative magnetic resonance (MR) imaging, spectroscopy, perfusion, and diffusion. Neuropsychological and behavioral assessments addressed the functional significance of our various neurobiological measures.
Results: In alcoholics, chronic smoking was associated with greater abnormalities in regional MR-based measures of neocortical gray matter volume, blood flow and neuronal viability, and poorer neurocognitive

performance. Chronic smoking was associated with poorer recovery of brain biology and cognition, particularly during short-term abstinence. In smoking alcoholics, greater neurobiological abnormalities were most prominent in frontal lobe and subcortical nuclei, which subserve emotional and behavioral regulation as well as executive skills, learning, and working memory.
Conclusions: Smoking alcoholics demonstrate poorer recovery of neurobiology during short-term abstinence than non-smoking alcoholics. This may affect the efficacy of behavioral and/or pharmacological interventions to reduce alcohol consumption. Concurrent participation in a smoking cessation program is advised for alcoholics, and pharmacological interventions should address both tobacco and alcohol consumption. Furthermore, examination of potential contribution of premorbid factors to differential recovery and treatment outcome is indicated.
Supported by RO1 AA10788

53. Neurobiological Correlates of Stress and Drug Craving are Predictive of Addiction Relapse Outcomes

Rajita Sinha

Yale University School of Medicine

Background: Addictive disorders are associated with high rates of relapse risk and treatment failure. Stress and drug cues are important factors influencing these clinical outcomes but mechanisms underlying this association are not well known. This presentation will examine whether there are neurobiological markers of stress and drug craving states that are associated with addiction relapse and treatment outcomes in alcohol and cocaine dependent individuals.
Methods: Human laboratory, brain imaging and clinical outcome approaches were used to assess stress neuroendocrine levels, gray matter volume changes and neural responses to stress and drug cue-induced craving in inpatient treatment engaged alcohol and cocaine dependent individuals. All patients were prospectively followed for 90 days post-treatment to assess relapse and after care treatment outcomes.
Results: Findings indicate that stress and cue-induced craving, altered cortisol and ACTH basal tone and blunted responsivity and lower prefrontal gray matter volume were each predictive of relapse risk. Furthermore, disrupted prefrontal responses to relaxed and stressful imaginal cues were predictive of drug craving and of increased risk of relapse. Increased post-treatment anxiety and drug craving was also significantly associated with engagement in follow-up outpatient treatment.
Conclusions: The findings identify multimodal neurobiological markers of altered stress and high craving states that are sensitive to addiction relapse risk and clinical outcome. These data will be discussed in the context of identifying those who may be most vulnerable to these neurobiological alterations, as well as implications for treatment development strategies that target stress and drug craving states to improve addiction relapse outcomes.
Supported by P50-DA016556; R01-AA013892; UL1-DE019586

SYMPOSIUM
Investigating Repetitive Transcranial Magnetic Stimulation (rTMS) with Functional Brain Measures

Thursday, May 20, 2010 3:00 PM - 5:00 PM
Location: Maurepas - 3rd Floor
Chair: F. Andrew Kozel*
Co-Chair: Mark S. George**

*Supported by NIMH 5K23MH070897-04; Grant-in-kind from Neuronetics, see individual abstracts for their disclosures
**Supported by VA CSP #556, 5R01MH069887 PI: George, Mark, 5R01MH069896 PI: George, Mark

54. RTMS and PET: Prediction of Response and Effect of Treatment

Robert M. Post

George Washington University

Background: Optimal rTMS parameters for individual depressed patients have not been defined. Previously, we found that high versus low frequency rTMS at 80% and 100% of MT produced opposite effects on mood in many depressed patients, and that depressed patients showed great variability in their patterns of baseline metabolism and blood flow on PET.
Methods: We studied the effects of two and three weeks of 5 times/week rTMS over left prefrontal cortex at 100% and 110% of motor threshold (MT), respectively, in patients with unipolar and bipolar depression.
Results: In contrast to the weak and inconsistent antidepressant effects of rTMS at 80% and 100% MT that we observed previously, at 110% both high and low frequencies were more effective at 3 weeks than a sham control procedure; and improvement became progressively marked with further extension of treatment from 3 weeks to 8 weeks. A series of high frequency (20Hz) rTMS produced lasting (72 hours or longer) and widespread increases in rCBF measured with O15 PET, while low frequency (1 Hz) rTMS produced decreases in rCBF throughout many brain regions. We evaluated whether those with baseline hypo-activity on PET would respond preferentially to 20Hz rTMS (to increase activity) while those with hyperactivity at baseline would respond preferentially to 1Hz (to decrease activity).
Conclusions: We found only partial confirmation of these predictions, and choice of optimal frequency for individual patients remains uncertain, particularly since intermediate frequencies of 10Hz are now being most widely utilized.
Supported by NIMH

55. TMS/fMRI: The Lessons we Have Learned about How to Better Treat Depression

Ziad S. Nahas

Department of Physiology and Neuroscience, Medical University of South Carolina, Charleston, SC

Background: Daily prefrontal rTMS was initially developed as a potential antidepressant with the working hypothesis that repeated stimulation of prefrontal cortex would also affect connected limbic regions and reset a prefrontal cortex-limbic circuit involved in mood regulation.
Methods: We scanned 23 depressed patients with the interleaved technique who were exiting phase I of a larger study. Phase I consisted of 3 weeks of either sham or real rTMS. We investigated 1) the local and prefrontal effects of TMS on the group as a whole, 2) whether mood state on the day of the scan affects this circuit activity, 3) whether depression state (remitters vs. non-remitters) influenced the activation, and 4) whether 3 weeks of real TMS results in different activation patterns than 3 weeks of sham.

Results: For the entire group (n=23), left prefrontal TMS resulted in activations in cortical as well as connected limbic regions. Significant changes were seen in R insula, bilateral prefrontal cortex (BA 9, 6, 8), bilateral cingulate gyrus (BA 24 and 25) as well as R parietal cortex (cuneus and precuneus). Higher intensity stimulation produced more activation. There was no significant difference between remitters and ill subjects. Small differences were found when covarying HRSD score on the day of the scan.
Conclusions: Left prefrontal TMS applied within the MRI scanner to the left prefrontal cortex in depressed patients causes changes in cortical as well as limbic connected regions visible with the interleaved TMS/fMRI technique. Future studies will focus on identifying acute prognosticators of good long-term clinical outcomes.
Supported by R01MH069887

56. Gamma Oscillations in Response to Repetitive Transcranial Magnetic Stimulation in Healthy Subjects and Patients with Schizophrenia

Zafiris J. Daskalakis[1], Mera S. Barr[1], Faranak F. Farzan[1], Lisa C. Tran[1], Paul B. Fitzgerald[2]

[1]Schizophrenia Program, Centre for Addiction and Mental Health, Toronto, ON, Canada, [2]Alfred Psychiatry Research Centre, Monash University, Melbourne, Australia

Background: Repetitive transcranial magnetic stimulation (rTMS) has been shown to induce neurophysiological changes in the cortex that can be recorded through electroencephalography. Oscillatory activity in the gamma (30-50 Hz) frequency range represents a neurophysiological measure that has been shown to be altered during working memory, a cognitive process that is mediated by the dorsolateral prefrontal cortex (DLPFC).
Methods: We examined the effect of 20 Hz rTMS applied bilaterally to the DLPFC on gamma oscillations elicited during the *N-back* working memory task in 22 healthy subjects and 24 patients with schizophrenia.
Results: Compared to sham rTMS, active rTMS produced a significant *increase* in gamma oscillations (p=0.001) in healthy subjects that was most pronounced in the 3-back condition, the condition associated with greatest cognitive demand. In patients with schizophrenia, by contrast, active rTMS reduced gamma oscillations compared to sham (p=0.012). Neither group demonstrated significant changes in other frequency ranges, suggesting that rTMS selectively modulates only gamma oscillations.
Conclusions: These findings suggest that patients with schizophrenia demonstrate altered gamma modulation in response to rTMS, a finding that may be related to an altered balance between inhibition and excitation in this disorder. As gamma oscillations are also closely associated with cognitive performance, these findings may also provide important insights into the mechanisms that lead to enhanced cognitive performance.
Supported by Canadian Institutes of Health Research; NARSAD; Ontario Mental Health Foundation

57. Using Functional Near Infrared Spectroscopy (fNIRS) to Measure Brain Changes Associated with rTMS

F. Andrew Kozel

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Background: Simultaneously acquiring functional Near Infrared Spectroscopy (fNIRS) during Transcranial Magnetic Stimulation (rTMS) enables brain function to be noninvasively assessed in all superficial cortical regions of the brain, as well as gain a greater understanding of the neurobiology of rTMS treatment parameters.
Methods: Healthy, nonmedicated adults were recruited from the local community. After written informed consent, they underwent two visits of simultaneous rTMS/fNIRS separated by 2 to 3 days. In each visit, the motor cortex and subsequently the prefrontal cortex (5 cm anterior to the motor cortex) were stimulated (1 Hz, max 120% MT, 10 s on with 80 s off, for 15 trains) while simultaneous fNIRS data were acquired from the ipsilateral and contralateral brain regions. The fNIRS data were analyzed to determine if the technique was reliable and if significant brain changes could be detected for the motor and prefrontal cortex.
Results: For the 11 participants studied, there was no significant difference in brain changes to rTMS between Visit 1 and Visit 2. Stimulation of both the motor and prefrontal cortices resulted in a significant decrease in oxygenated hemoglobin (HbO2) concentration in both the ipsilateral and contralateral cortices.
Conclusions: Simultaneous rTMS/fNIRS provides an objective and reliable measure of regional cortical brain activation and connectivity that could be very useful in studying brain disorders as well as cortical changes induced by rTMS. This technique could be used to assess an individual's brain function as well as changes induced by specific parameters in order to customize treatment.
Supported by NIMH 5K23MH070897-01; grant-in-kind Neuronetics for use of rTMS device and disposables

SYMPOSIUM
Automatic Emotion Control Circuitry: Dysregulations in Depression, Anxiety, Personality Disorders

Thursday, May 20, 2010 3:00 PM - 5:00 PM
Location: Bayside A - 4th Floor
Chair: Harold W. Koenigsberg*
Co-Chair: Kevin Ochsner**

*Supported by NIMH RO1-077813
**Supported by NIH R01MH076137

58. Expectancy of Emotion and its Changes in Depression

Georg Northoff

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Background: Patients with Major Depressive Disorder (MDD) suffer clinically from abnormal anticipation of predominantly negative emotions. While there have many imaging studies conducted in MDD, the exact neural mechanisms underlying such abnormal emotional expectancy remain unclear though.
Methods: We here present a series of fMRI studie son emotional expectancy and emotional perception. We ibnvestigated unmedicated patients with MDD and subjected them to a paradigm in fMRI where the perception of an emotional picture (4s) was preceded by an anticipation period of about 8-11s. Analysis of the data focused predominantly on the anticipation period and its effects on the subsequent perception period.
Results: MDD patients showed abnormally increased neural activity changes during the anticipation period in predominantly the perigenual anterior cingulated cortex (PACC) and the right dorsolateral prefrontal cortex (DLPFC). While they showed reduced activity in the left DLPFC. Interestingly, we also observed a correlation of the signal changes in these regions with the severity of depression as measured with the Beck Depression Inventory.
Conclusions: Our data show specific neural changes in especially the expectancy period in MDD in both medial and lateral prefrontal regions. Interestingly there also seems to be a dysbalance between right and left DLPFC during the anticipation period. The correlation with the BDI point to the clinical relevance of our findings.
Supported by CIHR, EJLB-Michael Smith

59. Sensitization and Habituation of Neural Networks in Response to Aversive Social Cues in Borderline and Avoidant Personality Disorder Patients

Harold W. Koenigsberg[1,2], Jin Fan[1], Xun Liu[1], Kevin Guise[1], Kevin N. Ochsner[3], Stephanie Guerreri[1], Antonia S. New[1,2], Marianne Goodman[1,4], Larry J. Siever[1,2]

[1]Mount Sinai School of Medicine, New York, NY, [2]James J Peters VA Medical Center, New York, NY, [3]Department of Psychology, Columbia University, New York, NY, [4]James J Peters VA Medical Center, New York, NY

Background: Intense emotional reactivity is a hallmark feature of Borderline Personality Disorder (BPD) and is associated with many of the disorder's most maladaptive features such as suicidality, intense anger, and unstable relationships. Avoidant Personality Disorder (AvPD) shares with BPD an excessive reactivity to social cues, but lacks the emotional instability. The neural bases of these emotional responses are poorly understood, but a failure to habituate or a sensitization to aversive social cues have been posited as underlying mechanisms.
Methods: 3.0 T BOLD fMRI images were obtained as patients with BPD (N=17), patients with AvPD (N=21), and healthy volunteers (HC's) (N=19) viewed novel and repeated presentations of neutral and aversive pictures depicting social interactions.
Results: When viewing repeated compared to novel aversive pictures, BPD patients showed greater activation in the right amygdala, fusiform gyrus, caudal anterior cingulate cortex (ACC), and left inferior frontal cortex, whereas HC's showed lesser activation. In contrast to BPD patients, AvPD patients showed greater activation in the caudal ACC when viewing novel pictures vs. repeat pictures.
Conclusions: These data suggest that in limbic, prefrontal and visual processing regions BPD patients sensitize to repeated presentations of negative social cues in contrast to HC's who habituate. AvPD's show a different pattern. The tendency to sensitize in the BPD's may account in part for the increased social reactivity of BPD patients in ongoing relationships. This study is the first to our knowledge to identify neural patterns distinguishing between two distinct personality disorders, characterized primarily by different types of social reactivity.
Supported by NIMH RO1 MH077813

60. Amygdala Habituation and Trait Anxiety in Adolescence

Todd Hare

Computation and Neural Systems Division, Humanities and Social Sciences Division, California Institute of Technology, Pasadena, CA

Background: Adolescence is a transition period from childhood to adulthood that is often characterized by emotional instability. This period is also a time of increased incidence of anxiety and depression, underscoring the importance of understanding biological substrates of behavioral and emotion regulation during adolescence. Developmental changes in the brain in concert with individual predispositions for anxiety might underlie the increased risk for poor outcomes reported during adolescence. We tested the hypothesis that difficulties in regulating behavior in emotional contexts in adolescents might be due to competition between heightened activity in subcortical emotional processing systems and immature top-down prefrontal systems. Individual differences in emotional reactivity might put some teens at greater risk during this sensitive transition in development.
Methods: We examined the association between emotion regulation and frontoamygdala circuitry in 60 children, adolescents, and adults with an emotional go-nogo paradigm. We focused on neural adaptation within this circuitry across time with functional magnetic resonance imaging.
Results: Adolescents showed exaggerated amygdala activity relative to children and adults. This age-related difference decreased with repeated exposures to the stimuli, and individual differences in self-ratings of anxiety predicted the extent of adaptation or habituation in amygdala. Individuals with higher trait anxiety showed less habituation over repeated exposures. This failure to habituate was associated with less functional connectivity between ventral prefrontal cortex and amygdala.
Conclusions: These findings suggest that exaggerated emotional reactivity during adolescence might increase the need for top-down control and put individuals with less control at greater risk for poor outcomes.
Supported by R01DA18879; F31MH073265

61. Medial Prefrontal 5-HT2A Receptors Predict Temporal Habituation of Threat-Related Amygdala Reactivity

Ahmad R. Hariri

Department of Psychology and Neuroscience, Duke University, Durham, NC

Background: Feedback inhibition of the amygdala via medial prefrontal cortex(mPFC) is an important component in the regulation of complex emotional behaviors. The functional dynamics of this corticolimbic circuitry are, in part, modulated by serotonin (5-HT). Serotonin 2A (5-HT2A) receptors within the mPFC represent a potential molecular mechanism through which 5-HT can modulate this corticolimbic circuitry.
Methods: We employed a multimodal neuroimaging strategy to explore the relationship between threat-related amygdala reactivity, assessed using blood oxygen level--dependent functional magnetic resonance imaging, and mPFC 5-HT2A density, assessed using [18F]altanserin positron emission tomography in 35 healthy adult volunteers.
Results: We observed a significant inverse relationship wherein greater mPFC 5-HT2A density was associated with reduced threat-related right amygdala reactivity. Remarkably, 25-37% of the variability in amygdala reactivity was explained by mPFC 5-HT2A density. We also observed a positive correlation between mPFC 5-HT2A density and the magnitude of right amygdala habituation. Furthermore, functional coupling between the amygdala and mPFC was positively correlated with 5-HT2A density suggesting that effective integration of emotionally salient information within this corticolimbic circuitry may be modulated, at least in part, by mPFC 5-HT2A.
Conclusions: Collectively, our results indicate that mPFC 5-HT2A is strongly associated with threat-related amygdala reactivity as well as its temporal habituation and functional coupling with prefrontal regulatory regions.
Supported by MH067602, MH064625, MH072837, DA023420, NARSAD

SYMPOSIUM
Human Studies of Oxytocin's Effects in Schizophrenia
Thursday, May 20, 2010 3:00 PM - 5:00 PM
Location: Oak Alley - 4th Floor
Chair: David Feifel*

*Supported by Stanley Medical Research Institute

62. Relationship of Neuroendocrine Dysfunction to Clinical Symptoms in Schizophrenia

Morris Goldman

Northwestern University

Background: A subset of schizophrenic patients experience potentially life-threatening water imbalance and exhibit hippocampal-mediated impairments in vasopressin, HPA axis and oxytocin activity. The latter impairment is proportional to their social dysfunction and their inability to correctly identify facial affects. Oxytocin has been shown to improve social function and diminish fear responses in humans and other mammals.
Methods: Intranasal oxytocin at 0, 10, and 20 IU was administered in randomized order to schizophrenic patients with (n = 5) and without (n = 9) water imbalance as well as healthy controls (n = 11) prior to assessing facial affect intensity.
Results: Only significant effect of oxytocin was with ratings of fear, with no effect in five other assessed emotions. Assessed fear fell with higher levels of intransal oxytocin in those with water imbalance, rose in those without water imbalance, and was unaffected in HC ($P < .001$).
Conclusions: Fear is the major emotion which schizophrenics cannot accurately assess and appears to be suppressed by oxytocin. These data support the view that patients with water imbalance have enhanced fear responses due to deficits in central oxytocin activity. Oxytocin agonists may have a therapeutic effect in this patient population.
Supported by NIH R21MH02295

63. Endogenous Oxytocin Correlates with Improved Clinical Symptoms in Schizophrenia

Leah H. Rubin, C. Sue Carter, Lauren Drogos, Hossein P. Pournajafi-Nazarloo, Pauline M. Maki

Department of Psychiatry, University of Illinois at Chicago, Chicago, IL

Background: Sex hormones are implicated in the pathogenesis of schizophrenia. Low levels of estrogen and oxytocin, hormones that may act as neuromodulators, are common in women with schizophrenia, and variations in these hormones affect cognitive functions (including social cognition) that are impaired in the disease. The aim of this study was to identify hormonal influences that contribute to variations in symptoms and social cognition in schizophrenia using a menstrual cycle paradigm.
Methods: Fifty women (30 healthy and 20 patients) completed assessments at two distinct phases of their menstrual cycle, and 54 men (27 healthy and 27 patients) completed testing at comparable intervals to the women.
Results: Estradiol and progesterone increased in all women, and clinical symptoms improved in female patients during the midluteal versus follicular phase. Cycle-related changes in symptoms were not significantly related to changes in any hormone. However, in female patients, higher levels of endogenous oxytocin and progesterone were associated with a less severe clinical presentation during the midluteal phase. In men, higher levels of oxytocin were associated with a less severe clinical presentation across both sessions. With respect to social cognition, women were more accurately able to identify emotional faces during the follicular compared to the midluteal phase. Higher levels of oxytocin related to perceiving faces as happier in both female patients (after adjusting for clinical symptoms) and controls.
Conclusions: Individual differences in oxytocin levels predict clinical symptoms in both men and women with schizophrenia. Higher levels of oxytocin are associated with improved social cognition in females with and without schizophrenia.
Supported by F31MH082480

64. Intranasal Oxytocin Added Adjunct to Antipsychotics Reduces Symptoms of Schizophrenia

David Feifel

University of California, San Diego

Background: Animal studies indicate that oxytocin produces antipsychotic-like effects and human studies suggest that intranasal oxytocin increases trust and pro-social behaviors in healthy humans. As such, we hypothesized that oxytocin may have therapeutic benefit for symptoms of schizophrenia and, in particular, may reduce features of paranoia and suspiciousness. The purpose of this study was to evaluate the efficacy and safety of intranasal oxytocin as adjunct therapy for schizophrenia patients maintained on a stable antipsychotic regimen.
Methods: This was a double-blind, randomized cross-over trial that enrolled schizophrenia patients whose symptoms were not fully controlled on current antipsychotic regimens as defined by a score of at least 55 on the PANSS and at least 4 (moderate) on the item 6 of the PANSS, which measures suspiciousness/persecution. The total study duration was 7 weeks: 3-weeks of daily treatment with adjunctive intranasal oxytocin (40 IU, twice a day) and 3-weeks of treatment with adjunctive placebo. Treatment sequence was randomly assigned and there is one week of washout between treatments.
Results: Total PANSS baseline scores at the start of each treatment arm were highly similar (80.8 and 80.6 but was significantly lower for adjunctive oxytocin (71.9) compared to placebo (76.7) ($p=0.006$ by paired t-test) at end point (3-weeks). There were no differences in rates of adverse events between placebo and oxytocin.
Conclusions: These preliminary results support the hypothesis that oxytocin has therapeutic effects on symptoms of schizophrenia and it may be an effective method of augmenting established antipsychotic medication.
Supported by Stanley Medical Research Institute

65. Oxytocin Treatment of Social Cognitive Deficits, Paranoia and other Psychotic Symptoms in Schizophrenia

Cort A. Pedersen[1], David Penn[2], Shane Rau[1], Kayvon Salimi[1]

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Background: Oxytocin (OT) stimulates prosocial behavior in animals and humans and also exerts antipsychotic-like effects in rodents. Social dysfunction, which is the most disabling and treatment resistant symptom of schizophrenia, has been linked to social cognition deficits and is exacerbated by paranoia.
Methods: We conducted a 2-week double-blind pilot study in schizophrenic patients comparing twice daily treatment with intranasal OT (24 IU/dose) vs. saline placebo (N = 5/treatment group) on psychotic symptoms and performance on a battery of social cognition tasks. Inclusion criteria included a diagnosis of paranoid or undifferentiated schizophrenia for > 1 year, PANSS total score > 60, PANSS suspiciousness/persecutory subscore > 4 and stability of psychotropic medications

and symptom for > 1 month. Subjects remained on their usual antipsychotic medications during the trial. Social cognition and psychiatric assessments were conducted at baseline and days 3, 7 and 14 of the trial.
Results: OT treatment, but not saline, produced changes from baseline to treatment day 14 that were significant, tended toward significance or corresponded to medium to large effect sizes. These included declines in total PANSS scores ($p < .01$), suspiciousness/persecutory subscores ($p = .09$) and Paranoia Scale self-ratings ($p = .12$) as well as improvements in second order theory of mind ($p = .07$) and trustworthiness ratings of faces ($p = .20$, eta-sq .37). Some measures are still undergoing analysis. Laboratory values and vital signs remained stable and no side effects occurred.
Conclusions: A 6-week treatment trial is underway to more adequately test the clinical efficacy of intranasal OT in schizophrenia.
Supported by R01 MH 077838, R01 MH051246-09, Foundation of Hope for Research and Treatment of Mental Illness, North Carolina Biotechnology Center

SYMPOSIUM
microRNAs: Novel Modulators of Neuronal and Behavioral Plasticity
Thursday, May 20, 2010 3:00 PM - 5:00 PM
Location: Grand Ballroom ABC
Chair: Husseini K. Manji
Co-Chair: Guang Chen*

*Supported by NIMH-IRP

66. Non-Coding RNAs in Schizophrenia

Claes Wahlestedt

The Scripps Institute

Background: The advent of systems biology marks the beginning of an era of conceptual integration in disease biology. The non-protein-coding transcriptome, including microRNAs, will play a formative role by emphasizing the flow of information through large macromolecular networks in complex diseases.
Methods: This study is part of an effort to assess, by microarray, RT-PCR and deep sequencing, schizophrenia associated alterations of microRNA and long non-coding RNA concentrations in prefrontal cortex (PFC) and other brain regions from three species; Mouse, Monkey and Human. Selected noncoding RNAs are subsequently studied functionally *in vitro* and *in vivo* in rodent models.
Results: miR-219 was reduced in mouse PFC tissues from mice after administration of dizocilpine (MK-801), Expression levels of miR-219 were also lower in PFC from mice with hypomorphic mutation in the NR1 subunit of the NMDA-R. Pretreatment with antipsychotic drugs, haloperidol or clozapine, prevented the reduction of miR-219 after dizocilpine injection. Mice receiving an LNA-modified antisense oligonucleotide to miR-219 displayed markedly altered hyperlocomotion and stereotypy in response to dizocilpine administration. Consistent with a role for miR-219 in NMDA-R signaling, we identified and validated CaMKIIgamma as an mRNA target of miR-219.
Conclusions: miR-219 negatively regulates the function of NMDA receptors. CaMKIIgamma, an integral downstream responder to NMDA signaling, is a target of miR-219 *in vitro* and *in vivo*. The silencing of miR-219 in murine brain releases the translational repression of the microRNA on CaMKIIgamma mRNA, thus providing a compensatory mechanism to maintain NMDA-R function during acute antagonism of the receptor and to attenuate associated behavioral manifestations.
Supported by RO1MH083733

67. Rapid Mechanisms of Molecular Tolerance

Andre Pietrzykowski

Department of Animal Sciences, Rutgers, The State University of New Jersey, New Brunswick, NJ

Background: One of the most reliable predictors of future alcohol abuse is an enhanced ability to recover from alcohol-induced performance deficits within a single session of alcohol drinking. This is known as acute tolerance. I will describe recent work on alcohol and the calcium- and voltage-gated BK channel, which plays an important role in alcohol tolerance. I will highlight varied players underlying molecular tolerance, focusing primary on our research demonstrating an important role for microRNA in the development of tolerance.
Methods: Our methodology combines state-of-the-art techniques of molecular biology with electrophysiological approach. Thus, we are able to monitor molecular events during drug exposure, and the functional consequences of these events.
Results: I will show that in adult mammalian brain, alcohol up-regulates microRNA (miR-9) and mediates post-transcriptional reorganization in BK mRNA splice variants by miR-9-dependent destabilization of BK mRNAs containing 3'UTRs with a miR-9 Recognition Element (MRE). Different splice variants encode BK isoforms with different alcohol sensitivities, and those predominating after the selective actions of miR-9 are relatively insensitive to alcohol. Computational modeling indicates that this miR-9 dependent mechanism contributes to alcohol tolerance. Moreover, this mechanism can be extended to regulation of additional miR-9 targets relevant to alcohol abuse, as well as in adaptation to other molecular stressors.
Conclusions: Our results describe a novel mechanism of regulation of stability of alternatively spliced mRNA by miRNA in drug adaptation and neuronal plasticity.
Supported by NIH

68. Opposite Effects of Chronic Exposure to Corticosterone and Antidepressants on miRNA Expression in the Hippocampus; Relevance to the Treatment of Mood Disorders

Peter Olausson

Department of Psychiatry, Yale University, New Haven, CT

Background: Chronic exposure to stress can produce depressive-like behavior and aberrant neuroplasticity within cortico-limbic-striatal brain regions in experimental animals. We have demonstrated that prior chronic exposure to the stress hormone corticosterone to rodents produces a persistent depressive-like state, characterized by behavioral despair, decreased motivation, anhedonia, and cognitive deficits. This behavioral phenotype is reversed by chronic antidepressant treatment (ADT), but the corresponding neurobiological mechanisms regulating altered plasticity after glucocorticoid exposure and its reversal by ADT are not well established. We therefore examined whether changes in the expression of microRNAs (miRNA), a class of non-coding RNAs that regulate protein translation, may contribute to these behavioral observations and the neurobiological substrate of stress-related mood disorders.
Methods: Rats were subjected to prior chronic exposure to corticosterone, the chemical antidepressant amitriptyline or to chronic electroconvulsive shock. The effects of these experimental manipulations on miRNA expression in hippocampus were examined with a combination of microarrays and quantitative real-time PCR.
Results: We identified a large number of regulated miRNAs with the vast majority showing opposite regulation after chronic corticosterone and ADT exposures. These observations suggest that changes in miRNA expression may contribute to alterations in protein expression after chronic stress, and to the pharmacological effects of ADT.
Conclusions: Together, these studies demonstrate that both stress and ADT

have the capacity to alter expression of miRNAs in hippocampus. They have also begun to identify specific miRNAs with possible relevance to the neurobiology of stress-induced mood disorders and their treatment, with the ultimate goal of finding novel therapeutic targets for depression treatment.
Supported by MH066172, NARSAD Young Investigator Award and Yale-IRCSSA Pilot grant

69. Roles of Selected miRNAs in Stress Coping and Behavioral Regulation Related to Mania

Guang Chen

NIMH/NIH

Background: microRNAs are known to regulate brain structural and functional plasticity. Stress can trigger mood disorder episodes. Chronic restraint stress in rodents causes hippocampal dendritic structural modifications, which can be prevented by chronic treatment with the mood stabilizer lithium. Therefore, we suspect that miRNAs are one of the potential converging points in the biological processes underlying stress coping and mood stabilizers' actions.
Methods: The hippocampal miRNA expression profiles of chronic lithium or valproate treatment and chronic restraint stress were analyzed using a microArray method and then validated by the qPCR method. The targets of affected miRNAs were predicted using picTar software. The behavior of mutant animals was evaluated using a battery of tests sensitive to mood disorder related changes.
Results: Mood stabilizers and stress produced opposing effects on two miRNAs, let-7b and miR221. A predicted let-7b target is M1 muscarinic receptor. Let-7b overexpression down-regulated and inhibition up-regulated M1 receptor levels in cerebral cortical cell culture. Lithium treatment, which down-regulated let-7b levels, increased M1 receptor levels in the brain. M1 KO mice display a cluster of phenotypes related to mania, which were partially rescued by chronic lithium treatment.
Conclusions: These data illustrated that let-7b, a convergent miRNA target of stress and mood stabilizers, regulates M1 receptor levels, and the M1 receptor is involved in behavioral regulation related to mania. The roles of miRNAs in stress coping and mediating the mood stabilizers' actions, as well as the mechanism through which miRNAs are regulated by stress and mood stabilizers, should be further investigated.
Supported by NIMH-IRP

SYMPOSIUM

Neurosteroids as Novel Therapeutics in Schizophrenia and other CNS Disorders

Thursday, May 20, 2010 3:00 PM - 5:00 PM
Location: Borgne - 3rd Floor
Chair: Christine E. Marx*
Co-Chair: E. Sherwood Brown**

*Supported by VA MIRECC, VA ARCD, NIH, NARSAD
**Supported by Stanley Medical Research Institute

70. Proof-of-Concept Randomized Controlled Trial with Pregnenolone in Mild Traumatic Brain Injury

Christine E. Marx

Duke University Medical Center and Durham VA

Background: Effective pharmacological interventions for mild traumatic brain injury (TBI) and co-occurring cognitive and anxiety symptoms are limited. Designated the "signature injury" of the Iraq and Afghanistan wars, new treatments for TBI and related sequelae are urgently needed. Targeting neurosteroids represents a logical therapeutic strategy. Neurosteroids demonstrate neuroprotective actions in rodent models of TBI, enhance learning and memory, and exhibit anxiolytic effects. We therefore investigated pregnenolone for cognitive and post-traumatic stress disorder (PTSD) symptoms in veterans with mild TBI.
Methods: Following a two-week placebo lead-in, veterans with mild TBI were randomized to pregnenolone (fixed, escalating dosing), or placebo, for eight weeks. The Brief Assessment of Cognition (BAC), Clinician-Administered PTSD Scale (CAPS), and other assessments were administered at baseline, 4 weeks, and 8 weeks.
Results: Of 30 patients randomized, 22 (73%) completed at least four weeks of treatment (11/group). Mean changes in composite BACS and total CAPS scores were not significantly different between groups. However, increases in pregnenolone (Spearman r=-0.85;p=0.0037), pregnanolone (r=-0.63;p=0.067), and allopregnanolone (r=-0.85;p=0.0037) were significantly correlated with reductions in total CAPS scores in the group randomized to pregnenolone. CAPS Cluster D symptom reductions also demonstrated significant correlations with neurosteroid increases post-treatment. Pregnanolone increases predicted improvements in resilience (CD-RISC; r=0.795, p=0.010). Cholesterol levels were significantly decreased post-treatment in the pregnenolone group compared to the placebo group (p=0.035).
Conclusions: Initial findings from this proof-of-concept investigation are encouraging and merit further study in larger cohorts. Neurosteroids may have utility both as interventions and candidate biomarkers for therapeutic response in mild TBI with co-occuring PTSD symptoms.
Supported by VA Mid-Atlantic MIRECC, NIH K23, VA ARCD, NARSAD

71. Multi-Year Continuation Study of Pregnenolone in Patients with Schizophrenia

Adam J. Savitz

Weill Cornell Medical College

Background: Pregnenolone is enriched in the brain and has multiple actions in vitro and in animal models. Pregnenolone was tested in a double-blind study in patients with schizophrenia on stable medications and in an open-label continuation study.
Methods: In the double-blind study, patients were randomly assigned to placebo, low dose, or high dose pregnenolone for 8 weeks. On completing the controlled study, 12 subjects continued in open treatment with pregnenolone.
Results: 24 of 32 subjects completed the trial with no different in side effects among the treatment groups. There were no changes in weight, abnormal movements, routine blood tests, or steroid levels other than pregnenolone. With the high dose, there was a significant reduction in negative symptoms as measured by the PANSS and the SANS (a 30% reduction) and improvement in verbal memory and attention. Five subjects remained on the pregnenolone for at least 3 years. Subjects felt that memory and concentration improved though objective cognitive tests did not change. The average SANS score changed from an initial score of 40 to 19.5 at 24 months with no further improvement in year 3. On the PANSS, there as a decrease in negative but not general and positive symptoms. All five improved functional level with increased employment or school attendance. One subject dropped out due to stomach upset, and one developed an enlarged prostate which may be related to pregnenolone.
Conclusions: A double-blind, placebo controlled trial of 500 mg of pregnenolone is ongoing to confirm these improvements in negative symptoms, functioning, and cognition.
Supported by Stanley Medical Research Insitute, GCRC of Weill Cornell Medical College

72. Pregnenolone for Mood and Cognition in Patients with Dual Diagnosis

E. Sherwood Brown

UT Southwestern Medical Center, Dallas, TX

Background: Mood and substance-use disorders are associated with cognitive deficits. Patients with mood and substance-use disorders have poorer cognition than patients with a mood disorder alone. Pregnenolone, a naturally occurring, over-the-counter, neurosteroid, may have beneficial effects on mood and cognition. In a pilot study, 70 participants with bipolar disorder or recurrent major depressive disorder and history of substance abuse/dependence were assigned randomly to pregnenolone (up to 100 mg/day) or placebo for 8 weeks.
Methods: Participants were assessed using the Hamilton Rating Scale for Depression (HRSD), Young Mania Rating Scale (YMRS), Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test (TMT-B), and Stroop Test. Mood symptoms were assessed bi-weekly, while cognition was evaluated at baseline, and at weeks 4 and 8. For the primary analysis, groups were compared using a random regression analysis that used all of the available data.
Results: The pregnenolone group, compared to placebo, showed trends toward greater improvement on the HRSD (p=0.09) and YMRS (p=0.07). A *post hoc* analysis of completers found a statistically significant reduction in HRSD scores with pregnenolone as compared to placebo (-11.6± 4.9 vs. -7.7±5.3, p =.03). Pregnenolone was well tolerated. Between-group changes in neurocognitive outcomes did not reach statistical significance.
Conclusions: The results suggest that pregnenolone may be associated with improvement in manic and depressive symptoms, but not cognition in depressed patients with a history of substance use. Larger trials examining the impact of pregnenolone on mood in a more narrowly defined clinical population are warranted.
Supported by Stanley Medical Research Institute

73. Augmentation with Dehydroepiandrosterone (DHEA) in Treatment-Refractory Schizophrenia

Lars Fredrik Jarskog

Columbia University, New York, NY

Background: N-methyl-D-aspartate (NMDA) receptor hypofunction is implicated in the pathophysiology of schizophrenia. DHEA is a neuroprotective neurosteroid known to enhance NMDA receptor function. Adjunctive use of DHEA was previously found to improve depression and negative symptoms in schizophrenia. It is not known if DHEA may have a therapeutic role in treatment-refractory schizophrenia. It was hypothesized that supraphysiological doses of DHEA could produce symptom improvement in treatment-refractory schizophrenia.
Methods: 30 male subjects with schizophrenia or schizoaffective disorder treated with atypical antipsychotics and were persistently symptomatic (PANSS 61-127) received either DHEA (up to 400 mg/d) or placebo for 6 weeks. PANSS, CGI, AIMS, SAS, Barnes ratings were performed weekly and DHEA and DHEA-S plasma levels were measured.
Results: Change in PANSS total scores between baseline and week 6 suggested a small advantage for subjects who received DHEA (-7.13 + 2.43, mean + SEM) compared to placebo (-2.25 + 2.85, p=0.202). Similar improvements in positive, negative and EPS ratings suggested a small advantage for DHEA-treated subjects. DHEA substantially increased DHEA and DHEA-S plasma levels. Although symptoms did not correlate with absolute DHEA or DHEA-S levels, the DHEA/DHEA-S ratio showed a modest correlation with symptom response.
Conclusions: This small proof-of-concept study provides encouraging though preliminary data that supraphysiological doses of DHEA may benefit patients with treatment-refractory schizophrenia. Given preclinical evidence that DHEA also exerts neurotrophic functions, larger studies with longer treatment duration are needed to better define the potential range of benefits for DHEA in schizophrenia.
Supported by Stanley Medical Research Institute

SYMPOSIUM
Astrocytic Dysfunction and Major Depression
Thursday, May 20, 2010 3:00 PM - 5:00 PM
Location: Grand Chenier - 5th Floor
Chair: Gustavo Turecki*
Co-Chair: Gerard Sanacora**

*Supported by CIHR
**Supported by R01 MH081211

74. Fine Anatomical Features of White Matter Astrocytes in Depressed Suicides

Naguib Mechawar

McGill University, Verdun, QC, Canada

Background: Several lines of evidence suggest that mood disorders are accompanied by altered cellular function and plasticity in the gray matter of key limbic brain regions. Recent studies have indicated that white matter integrity may also be affected. Given that astrocytes are increasingly implicated in mood disorders, we hypothesized that white matter astrocytes in the anterior cingulate cortex would display altered morphological properties in depressed suicides. To test this hypothesis, we compared the processes projected by these cells to those found in matched controls.
Methods: Postmortem BA24 samples from well-characterized depressed suicides and matched sudden-death controls were obtained from the Quebec Suicide Brain Bank. Fixed tissue blocks from the right hemisphere were stained using a standard Golgi protocol. Astrocytic processes were traced, reconstructed and quantified using a computer-based cell tracing system (Neurolucida).
Results: Although the average number of processeses per fibrous astrocyte was similar between groups, the average length of these processes was almost twice as long in depressed suicides (p = 0.0009). Sholl analysis revealed that this resulted in an overall increase in process length that was most significant in radii ranging from 30-80 µm around the cell body.
Conclusions: These results indicate that BA24 fibrous astrocytes project longer processes in depressed suicide, suggesting a more widespread influence for each of these white matter glial cells.
Supported by FRSQ

75. Astrocytic Glutamate Clearance: Relationship to Stress-Related Pathophysiology and Mechanism of Antidepressant Action

Gerard Sanacora

Yale University

Background: Glia dysfunction and abnormal glutamatergic neurotransmission are implicated in the neuropathology of stress-related illnesses including major depressive disorder. However, it is unclear whether a decrease in glial related glutamate uptake plays a direct role in the expression of depressive symptoms and whether increasing glial mediated glutamate uptake has an antidepressant action.
Methods: Heterozygous GLT1 (EAAT2) knockout mice and rats exposed to various periods of chronic unpredictable stress (CUS) were examined. Animals were treated with various doses of riluzole, a drug with effects on glutamate up take and release, given IP and the EAAT blocker Dihydrokainate (DHK) was administered directly into the infra-limbic PFC. Behavioral effects of the treatments were evaluated with sucrose preference test (SPT), active avoidance tests (AAT), and forced swim test (FST). Effects on amino acid neurotransmitter metabolism and glutamate cycling were evaluated with 13C-MRS measures.

Results: We demonstrate that drugs such as riluzole that have effects on glutamate uptake and release can reverse or prevent the effects of CUS on glial metabolism, glutamate cycling, and behavior. We also observed early evidence suggesting the heterozygous GLT1 knockout mice have behavior more similar to stressed animals than wildtype littermates, and that riluzole's antidepressant-like effects is reduced in these animals. Furthermore, we were also able to demonstrate that DHK injections into the PFC we are able to increase sensitivity to stress and decreased the antidepressant-like efficacy for riluzole.
Conclusions: Together, these results suggest modulation of glial mediated glutamate clearance may be a viable target for future antidepressant drug development.
Supported by NIMH-R01 MH081211

76. Dysfunction of an Astrocytic Gene Network in Major Depression and Suicide

Gustavo Turecki

McGill University

Background: Major depression and suicide are important public health problems that result from the interaction of different factors. While it is known that particular neurobiological processes underlie the emotions and actions leading to suicide, there is limited knowledge about the specific factors involved.
Methods: Using a non-biased subgroup analysis approach, we identified a network of astrocyte genes downregulated in frontal cortex of suicide completers compared to control subjects. These results were studied and further explored using a combination of neuroanatomic, molecular and functional techniques
Results: We found severely decreased levels of astrocyte-related genes Cx30, Cx43, FGFR3, SLC1A3, and GLUL in the suicide brain. These findings were externally and independently validated in a different dataset. Molecular and neuroanatomical studies did not indicate that reduced astrocyte number accounted for these results. We identified a previously unknown function for Sox9 as a transcription factor affecting this network and accounting for its downregulation.
Conclusions: These results suggest that functional alterations of astrocytes may underlie the suicide process and provide further evidence implicating astrocytes in the regulation of mood and psychopathology.
Supported by CIHR79253

77. Using Magnetic Resonance Spectroscopy to Probe Glutamatergic Neurotransmission in Mood Disorders

Dost Ongur

Harvard University/McLean Hospital

Background: Following its release into the synapse as a neurotransmitter, glutamate (Glu) is taken up by glial cells and converted to glutamine (Gln) which is shuttled back to neurons. Our group has been probing glutamatergic neurotransmission as one outcome of glial abnormalities in bipolar disorder.
Methods: We use a J-resolved proton magnetic resonance imaging sequence optimized for separate Glu and Gln detection on a 4 Tesla Varian scanner. Data are collected from 2x2x2cm voxels in the anterior cingulate cortex and parieto-occipital cortex. MRS data are quantified using LC Model. The Gln/Glu ratio is our main outcome measure because it is believed to reflect the dynamics of neurotransmitter release and handling.
Results: Acutely manic bipolar disorder patients have elevated Gln/Glu ratio in both brain regions compared with healthy controls. Other groups have reported reduced Gln/Glu levels in patients with major depression. We have found that the putative glutamatergic medication riluzole is effective in bipolar depression. It also raises the Gln/Glu ratio at day 2 of treatment but by 6 weeks this ratio returns to baseline. In collaboration with Dr. Jordan Smoller we have found a haplotype of 4 single nucleotide polymorphisms in the glutaminase gene (converts Gln to Glu) which shows a significant association with the Gln/Glu ratio.
Conclusions: The Gln/Glu ratio is dynamically modulated during mood episodes and during treatment with a glutamatergic agent. Polymorphisms in the neuron-specific enzyme which converts Gln to Glu are associated with Gln/Glu ratios. The implications of these findings for glial cell function in mood disorders will be discussed.
Supported by K23 MH079982

SYMPOSIUM
Enabling Medication Development for Addiction
Thursday, May 20, 2010 3:00 PM - 5:00 PM
Location: Grand Couteau - 5th Floor
Chair: Anne Cramer Andorn*
Co-Chair: Curtis Wright**

* Full Time Employee of GlaxoSmithKline
**Supported by Rock Creek Pharmaceuticals Inc.

78. Enabling Medication Development: Translating from Preclinical to Clinical Imaging

Linda J. Porrino

Wake Forest Univeristy, Winston-Salem, NC

Background: One of the important problems in the translation of preclinical data to the clinic has been the difficulty of extrapolating from rodent models of substance abuse directly to clinical efforts with human patients. The purpose of this presentation is to describe the development of a strategy that employs behavioral pharmacological approaches in rodents and nonhuman primates complemented by imaging with positron emission tomography to translate preclinical findings to clinical endpoints.
Methods: Medications are evaluated in rodent and nonhuman primate models to measure how candidate medications affect consumption and price of abused substances, along with assessments of their biological consequences of chronic administration. These strategies are complemented by PET imaging of receptor changes and functional activity.
Results: Data will be presented on two candidate medications. We will describe data in rodent models of self-administration and how these correspond to nonhuman primate measures. We have recently completed studies of the effects of agonist therapy with amphetamine and the GABA drug, baclofen, on behavioral endpoints. We will then focus on PET imaging functional brain activity of models of cue-induced craving, self-administration, and cognitive performance. Our data highlight issues of tolerance, route of administration and side effects on cognitive performance that accompany the administration of these candidate medications.
Conclusions: We have developed a strategy that may more reliably allow translation to the clinic.
Supported by NIH DA06634

79. Enabling Medication Development: Defining Phenotypes through Clinical Imaging

Anna Rose Childress[1,2], Teresa R. Franklin[1], Jesse J. Suh[1,2], Ronald N. Ehrman[1,2], Yin Li[1,2], Ze Wang[1,2], Marina Goldman[1], Kyle Kampman[1], Anita V. Hole[1,2], Anna R. Fornash[1,2], William Jens[1], Daniel Willard[1], Rebecca Hazan[1], Robert Fabianski[1], Ryan Carson[1]

[1]Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, [2]VA VISN 4 MIRECC, Philadelphia, PA

Background: One of the significant challenges in medication development is the striking heterogeneity of treatment response across individuals with the same descriptive phenotype, e.g., "cocaine dependence". Clinical imaging now offers an appealing tool for addressing this challenge: by discovering the brain endophenotypes contributing to clinical response heterogeneity, heterogeneity can be re-cast as a friendly catalyst for individualized, highly-effective treatments. This presentation will offer an empirically-derived "cue-reactive" endophenotype -- revealed through neuroimaging -- that may be used to parse clinical heterogeneity and guide medication development.
Methods: Cocaine (n=25, ongoing) and nicotine (n=45, ongoing)-dependent individuals were exposed to drug-related and non-drug (cues), using either BOLD (Blood Oxygen-Level-Dependent) or Arterial Spin-Labeled (ASL) Functional Magnetic Resonance Imaging at 3T. Data were analyzed within SPM, thresholded at $p<0.01$ for examination of five *a priori* reward-relevant regions of interest. Limbic activation to cues was examined in relation to 1) a clinical phenotype of "rapid relapse", 2) dopamine transporter (DAT) genetics, and 3) possible epigenetic influences (e.g., "trauma exposure").
Results: Cocaine patients with a "rapid" relapse phenotype exhibited greater limbic activation to cocaine cues, and poor connectivity between limbic and frontal (modulatory) regions; patients reporting prior trauma were also highly cue-reactive. Smokers who carried the DAT 9 polymorphism (enhanced dopamine signaling) had significantly enhanced limbic response, as compared to 10/10 homozygotes.
Conclusions: The "cue reactive" endophenotype revealed through brain imaging may be used to screen brain-targeted candidate medications, and to effectively parse clinical response heterogeneity.
Supported by (P50-DA12756, P60-DA-005186, R21-DA026114, R01DA025906); VA VISN 4 MIRECC; Alexander Foundation

80. Enabling Medication Development: Optimizing Dosage Using Preclinical and Clinical Imaging

John David Beaver

Clinical Imaging Centre, GlaxoSmithKline, London, United Kingdom

Background: Establishing whether a new molecule is reaching its intended target and gaining confidence in its pharmacological actions are major challenges in the development of candidate drugs for the treatment of addiction. Here we meet these challenges by integrating preclinical and clinical imaging in the early development of selective D_3 receptor antagonists.
Methods: *Primate:* In total 12 [^{11}C]PHNO PET scans were conducted (6 baseline and 6 post-dose) in 3 anaesthetised baboons. Four different dose levels of a selective D_3 antagonist were delivered intravenously as a bolus + infusion prior to post-dose scans.
Human: The amount and time-course of D_3 receptor occupancy (RO) following oral doses of the same D_3 antagonist were examined in healthy males. Baseline and up to two post-drug [^{11}C]PHNO PET scans were conducted in each subject. Post-drug scan times and dose levels (up to the maximum tolerated dose) were varied across subjects.
Results: Regional occupancies were calculated as the difference between baseline and post-drug [^{11}C]PHNO binding. In both primate and human, the highest [^{11}C]PHNO binding was in substantia nigra, followed by the globus pallidus and ventral striatum. We found dose-dependent reductions in [^{11}C]PHNO binding in each of these regions. A model was fit to relate plasma drug concentrations to D_3 RO. This model identified concentrations producing 50% and 90% of maximal occupancy.
Conclusions: These findings demonstrate that our novel D_3 antagonist reaches its intended target at doses considered safe for administration in human and identify an optimal dose for future proof of concept testing.
Supported by GlaxoSmithKline

81. Enabling Medicine Development: Use of the Human Laboratory for Preliminary Proof of Efficacy

Stephanie S. O'Malley

Yale University School of Medicine, New Haven, CT

Background: Researchers have developed laboratory paradigms to model components of addiction that are potential targets of pharmacotherapies, including the positive reinforcing effects of abused drugs, the conditioned rewarding effects of drug related cues, and negative-reinforcement. Examples include self-administration studies, cue exposure paradigms, and reinstatement models. Once validated with drugs demonstrated to be efficacious in the clinic, these laboratory models could be used for preliminary proof of efficacy with new drugs. Further evidence of predictive validity would include failure to observe effects of medications found to be ineffective in the clinic.
Methods: To illustrate these points, the results of several studies using an alcohol self-adminstration paradigm (O'Malley et al, 2003) testing different medications (naltrexone, rimonabant, memantine and varenicline) and corresponding findings from clinical trials will be presented. In this paradigm, subjects consume a priming dose of alcohol and then have the opportunity to self-administer additional drinks or keep a small payment per drink for every drink refused.
Results: Naltrexone reduced the number of drinks consumed in the laboratory, paralleling clinical findings. The model was sensitive to dose and individual differences in response (e.g., family history of alcoholism). Other compounds (e.g., varenicline) reduced drinking, and compounds that did not reduce drinking in the laboratory were ineffective in clinical trials at the doses studied.
Conclusions: The alcohol self-administration paradigm appears to be a valid method for obtaining preliminary evidence of efficacy for drugs intended to reduce drinking. Other models may be better suited to testing drugs that alter other aspects of addiction.
Supported by KO5-AA014715;P50AA12870;R01AA015596;NIAAA

ORAL SESSION
Mood Disorders
Thursday, May 20, 2010 3:00 PM - 5:00 PM
Location: Southdown - 4th Floor
Chair:See Program Book

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82. Neurogenesis Dependent Modulations of Neuroplasticity in Cornu Ammonis Regions of the Adult Hippocampus

Nicholas Hardy, Dennisse Jimenez, Keri Martinowich, **Robert J. Schloesser**

LMP, NIMH, Bethesda, MD

Background: Changes in adult hippocampal neurogenesis are linked to stress and required for behavioral responses to antidepressants. Stress decreases proliferation of adult hippocampal progenitor cells while antidepressants increase neurogenesis. In turn, animals without adult hippocampal neurogenesis show an increased corticosterone response. Newborn granule cells extend their axons into

the cornu ammonis region 3 (CA3). In this study we examined the effects of loss of newly born neurons on neuroplasticity in CA3.
Methods: We developed a transgenic mouse with herpes simplex virus thymidine kinase gene (HSV-tk) expression under control of the human GFAP promoter (hGFAPtk mice). In these mice we can conditionally suppress adult neurogenesis by administering p.o. valganciclovir (VGCV). We examined whether loss of newly born neurons would affect neuroplasticity in the CA3 region. We first utilized whole genome microarrays to screen for mRNA expression changes and subsequent qPCR validation. Secondly, we analyzed neuroanatomical parameters in CA3 using computer-assisted software to make stereological and volumetric cell measurements.
Results: Proliferation of cells in the adult CNS is decreased in the dentate gyrus of hGFAPtk mice treated with VGCV while proliferation in other areas, including the CA3 region of the hippocampus is unaffected. Analysis of microdissected CA3 showed changes in mRNA expression of several neuroplasticity-related genes. While the majority of measurements showed no differences, there were several selective changes in measures of neuroplasticity.
Conclusions: We identified several candidate genes as well as histological and neuroanatomical parameters in CA3 that were dependent on intact neurogenesis.
Supported by NIMH, NARSAD

83. Highly Selective GSK3 Inhibition Modulates Affective Behaviors in Mouse

Tracey Petryshen[1,2,3], Michael Lewis[1,2], Jennifer Pan[2], Elizabeth Clore[1,2], Erin Berry-Scott[1,2], Misha Riley[1,2], Ed Holson[2], Stephen Haggarty[2,4,5]

[1]Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, [2]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, [3]Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, [4]Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, [5]Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Background: Lithium is a first-line treatment for bipolar disorder (BP) that is superior to other mood stabilizers in preventing relapse. However, lithium's narrow therapeutic index, adverse reactions, and lack of response in one-third of BP patients highlights the critical need for improved medications. We are examining inhibitors of GSK3B, a direct and indirect target of lithium, to identify compounds that have a similar mechanism of action as lithium but greater selectivity to minimize adverse effects.
Methods: GSK3B inhibitors selected from the literature or cell-based small molecule screens were investigated in inbred mouse strains for modulation of behaviors modeling BP symptoms and/or having pharmacological validity, including amphetamine-induced hyperactivity, the forced-swim test (FST), and the progressive ratio test of motivated behavior. The mechanism of GSK3B inhibition was examined by biochemical and immunohistochemical analyses of brain tissue.
Results: Acute intraperitoneal administration of a highly potent and selective GSK3B inhibitor significantly reduced amphetamine response and was anti-depressive in FST to a greater degree than lithium. The effective dose was well below tolerability limits and concentrations that inhibit other kinases in vitro. Intracerebroventricular administration also attenuated behavior, indicating the effects are centrally mediated. Western blot confirmed increased inhibitory Ser9 phosphorylation of GSK3B in striatum of treated mice.
Conclusions: Highly potent and selective GSK3B inhibition is an effective mechanism of action for next generation BP therapeutics. This study identified a selective GSK3B inhibitor that attenuates behaviors modeling BP symptoms. Further examination of novel inhibitors from small molecule screens may identify additional potential therapeutics for BP treatment.
Supported by Stanley Medical Research Institute

84. Drugs that Stimulate Oxytocin Release Promote Social Bonding in an Animal Model Relevant to Autism

Meera E. Modi, Larry J. Young

Department of Psychiatry, Emory University, Atlanta, GA

Background: Oxytocin (OT) has been suggested as a treatment for the social deficits associated with autism. However, the therapeutic potential of oxytocin is limited by its poor penetration of the blood-brain-barrier. An alternative approach to modulating the OT system is to pharmacologically enhance endogenous OT release. Here we use social bonding in the prairie vole, assayed by the partner preference paradigm (PPP), to assess the prosocial effects of drugs that stimulate OT release. Alpha-melanocyte-stimulating-hormone (alpha-MSH) and serotonin (5-HT) act on oxytocinergic neurons to stimulate OT release. To target these systems, we administered Melanotan I/II (MTI, MTII; MC 3/4 R agonists) and busprione (BUS; 5-HT1a R agonist) to prairie voles. We hypothesized that administration of these drugs would accelerate bonding. If our hypothesis is correct, then we predict that a similar pharmacological approach may be used to enhance social cognition in humans.
Methods: MTI (1 and 10 mg/kg), MTII (1 and 10 mg/kg), BUS (8 and 30 mg/kg) or vehicle were administered peripherally to female prairie voles. Following cohabitation, the females were tested for social bonding using the PPP.
Results: Females receiving the high dose of MTII and the low dose of BUS formed robust partner preferences. MTI did not effect preference formation in this paradigm.
Conclusions: Drugs that targeted two different systems via receptors on OT neurons induced preference formation under conditions in which bonding does not typically occur. Therefore we suggest the prosocial effects of OT can be mimicked by drugs that stimulate endogenous OT release.
Supported by MH064692 (LJY); Autism Speaks Predoctoral Fellowship (MEM)

85. Prenatal Influenza Infection Alters Offspring Brain Development: Diffusion Tensor Imaging (DTI) Tractography of White Matter Pathways in the Rhesus Monkey

Sarah J. Short[1], Christopher L. Coe[2], Yundi Shi[1], Hongtu Zhu[3], Rebecca Knickmeyer[1], Martin Styner[4], John H. Gilmore[1]

[1]Department of Psychiatry, University of North Carolina, Chapel Hill, Chapel Hill, NC, [2]Department of Psychology, University of Wisconsin, Madison, Madison, WI, [3]Department of Biostatistics, University of North Carolina, Chapel Hill, Chapel Hill, NC, [4]Department of Computer Science, University of North Carolina, Chapel Hill, Chapel Hill, NC

Background: Maternal flu infection during pregnancy may be a risk factor for altered fetal brain development. An association between influenza and neurodevelopmental disorders, such as schizophrenia, is hypothesized from both rodent and retrospective human studies. Our research with primates has recently identified structural alterations in the brains of offspring following maternal influenza infection: reduced total gray matter and increased cingulate white matter (WM) volumes. Brain development in these offspring is further characterized in the current study using DTI to examine the organization and myelination of several WM tracts.
Methods: Ten pregnant rhesus monkeys were infected with a human-derived influenza virus, A/Sydney/5/97(H3N2), at week 17 post-conception (late 2nd trimester) and compared to 5 control pregnancies. Structural MR imaging and DTI (3T) were preformed at 13mos. (equivalent to late childhood). Automatic atlas-based methods determined regions and fiber tracts for analyses of WM organization and myelination. DTI parameters included fractional anisotropy

(FA), mean (MD), axial (AD) and radial (RD) diffusivities.
Results: Compared to Controls, regional analyses show Flu-animals have less organized WM, bilaterally in the visual region of the Temporal lobes. Tract based analyses highlight focal differences along several fiber tracts including: Genu, Thalamocortical radiations, Inferior-Longitudinal-Fasciculus, Cingulum, Uncinate, Pons-Occipital.
Conclusions: These findings demonstrate that a moderate viral infection during pregnancy can alter neural development. Alterations in myelination cannot be discerned from the current pattern of findings. However, DTI parameters indicate reduced fiber organization in specific regions and along particular tracts in Flu-exposed offspring. Overgrowth of WM is a possible explanation for these findings.
Supported by NIAID (AI067518); NIMH (F31 MH076606); NICHD (HD383386); UNC Conte Center for Schizophrenia Research (MH064065); UNC Neurodevelopmental Disorders Research Center (HD 03110)

86. Epigenetic Regulation of Serotonin Transporter and Stress Adaptation in Humans and Non-Human Primates

Erin L. Kinnally[1], Jeremy D. Coplan[2], Maria A. Oquendo[1], J. John Mann[1]

[1]Psychiatry, Columbia University, New York, NY, [2]Psychiatry, SUNY Downstate Medical Center, New York, NY

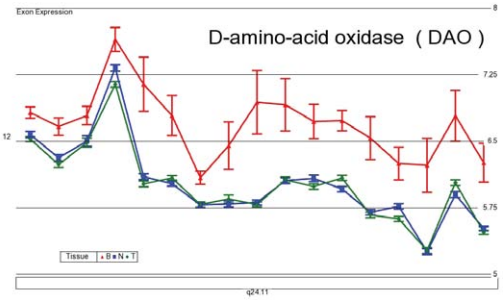
Background: Variation in the regulatory region of the serotonin transporter (*5-HTT*) gene moderates the effects of early life stress on stress adaptation, a hypothesized predictor of mood disorders. We assessed the role of early life stress, the serotonin transporter promoter polymorphism (*5-HTTLPR*), and methylation within a CpG island that overlaps with the 5-HTT transcription initiation site in depression severity in humans and stress reactivity in a complementary non-human primate model.
Methods: Depressed and healthy humans were genotyped for *5-HTTLPR*, *5-HTT* CpG methylation assessed from peripheral blood DNA using sodium bisulfite pyrosequencing, and childhood stress and depression severity recorded during diagnostic interview. Adult bonnet macaques were also genotyped for *5-HTTLPR* and *5-HTT* methylation status assessed. Further, stress reactivity, a hypothesized endophenotype for mood disorders, was observed in macaques that had experienced an experimental early life stressor (variable foraging demand) or control conditions.
Results: In both species, higher *5-HTT* CpG methylation conferred risk for poorer psychological outcomes in individuals that experienced early life stress. A methylation x environment interaction predicted depression severity in humans (backward multiple regression: (F (3, 59) = 3.147 , p = .032), and behavioral stress reactivity to both low (F (1,26) = 9.19, p = .006) and high (F (2,24) = 3.84, p =.036) intensity stressors in bonnet macaques. Interactions involving genotype were not observed.
Conclusions: These results suggest that *5-HTT* methylation status moderates the effects of early life stress on psychological outcomes, and that these processes are highly conserved across species.
Supported by P50 MH062185

87. Comparison of Blood and Brain Transcriptome

Marquis P. Vawter[1], Brandi Rollins[1], Adolfo Sequeira[1], Linda Morgan[1], Maureen Martin[1], William E. Bunney[2]

[1]Psychiatry and Human Behavior, Functional Genomics Laboratory, University of California, Irvine, Irvine, CA, [2]Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA

Background: The search for biomarkers in psychiatry has evolved from single analyte towards a more comprehensive transcriptomic and proteomic profiling. There has been little overlap in peripheral biomarkers, although multiple papers have been published in this area few studies have been reproducible across laboratories. In schizophrenia, some reported biomarkers, for example SELENBP1 and DAO mRNA levels have been reported to be altered in blood. This study reports LCL, PBMC, and brain correlations across samples for schizophrenia candidate genes.
Methods: The transcriptome was profiled with a high density exon array in whole blood, PBMC, lymphoblastoid cell line and brain tissue.
Results: Our data provides evidence that some biomarkers are present in high levels in both blood and brain, and do not appear to be merely a 'carry-over' effect of residual blood within the postmortem brain. Data will be presented from the top 10 GWAS candidate genes for schizophrenia to show levels in brain and blood of gene expression. We have conservatively estimated about 15% of transcripts might be useful as peripheral biomarkers in psychiatric disorders, examples are DAO and CHRNA7. Splicing isoforms in schizophrenia candidate genes such as NRG1 appear differentially expressed in blood and brain.
Conclusions: Biomarker combinations in blood may offer a window into brain transcriptome levels but only for a certain percentage of transcripts.Noting the pace of biomarker research of the peripheral transcriptome is easily measured at a low cost, this data can be further integrated with SNPs and CNV data for functional discovery. One limitation is that brain specific genes will not be tested in this biomarker approach. This limits the discovery of certain genes and utilization as biomarker.



This figure shows the relative levels of D-amino-acid oxidase (DAO) gene expression in brain (red), blood (blue), and cell lines (green).
Supported by R21MH074307

88. Unmedicated First-Episode Schizophrenia and Psychotic Bipolar Patients Show Reduced Neural Activation during Working Memory Maintenance

James L. Reilly, Anna-Maria D'Cruz, Sarah Keedy, Bruce McDonough, Peter J. Weiden, John A. Sweeney

Center for Cognitive Medicine, University of Illinois at Chicago, Chicago, IL

Background: Impaired working memory is an established neurocognitive deficit in schizophrenia that implicates prefrontal circuitry dysfunction. The specificity of this deficit to schizophrenia vs. psychotic bipolar disorder is unknown and is of interest given common risk genes and neurobiological abnormalities observed between these disorders.
Methods: We used an event-related fMRI design to examine brain activation during an oculomotor delayed response task, a translational working memory task that requires maintenance of spatial information over a delay period after which a saccade is made to the remembered location. Patients with schizophrenia or psychotic bipolar disorder who were early in their course of illness and unmedicated at the time of testing were compared to matched healthy individuals. Activation during the maintenance and response periods was contrasted with a passive central fixation period.
Results: Healthy individuals demonstrated robust activation during the maintenance period in several prefrontal cortical regions including the middle frontal gyrus and anterior cingulate, and the frontal and parietal eye fields,

while schizophrenia and psychotic bipolar patients failed to show significant activation in these regions. In contrast all three groups demonstrated comparable activation in sensorimotor regions, including frontal, supplementary, and parietal eye fields, during the response phase when saccades were made to remembered locations and to a corrective feedback target.
Conclusions: These findings indicate that first-episode schizophrenia and psychotic bipolar patients fail to activate prefrontal and parietal regions critical for maintenance of information to accurately guide subsequent responses, and suggest a shared prefrontal systems dysfunction underlying deficient working memory between these disorders.
Supported by K23MH083126; NARSAD

89. Lobar Volume Reductions and Psychotic Symptoms in People at High Genetic Risk of Schizophrenia

Stephen Lawrie

Psychiatry, University of Edinburgh, Edinburgh, United Kingdom

Background: Structural differences between the brains of people with schizophrenia and matched controls are highly replicated and the changes over time in people developing schizophrenia can be demonstrated, but the time-scale, causes and clinical correlates of these changes remain to be established.
Methods: We have developed automated parcellation techniques and applied them to all 495 structural MRI scans acquired with two machines over the ten years of the Edinburgh High Risk Study. We have remapped the T1-weighted intensity profiles based upon SPM tissue classification to reduce the susceptibility of the machine tracing to re-scan variations and change in scanner manufacturer. We integrated hand tracing protocols into a deterministic machine process to provide a highly repeatable method for extracting pre-frontal and temporal lobe volumes.
Results: The mean ICC across scan 1 and scan 2 on the same machine was 0.98, and was 0.975 across the scanner change between scans 3 and 4. People at high risk of schizophrenia had significantly greater reductions than the control group for the whole brain volume, left temporal lobe and left prefrontal lobe. The high risk subjects who developed schizophrenia showed significantly greater tissue loss in the left prefrontal lobes than the other high risk groups. Similar results were seen for the right prefrontal lobe. The extent of these changes was significantly correlated with increasing severity of delusions and hallucinations.
Conclusions: We demonstrate, we believe for the first time, associations between lobar volume reductions and increasing psychotic symptom severity as people develop schizophrenia.
Supported by NARSAD

POSTER SESSION
Mixed Topics
Thursday, May 20, 2010 5:00 PM - 6:30 PM
Location: Grand Ballroom DE

90. Effects of Memantine and Donepezil on Object Recognition Memory and Hippocampal Acetylcholine Levels in Rats with Cholinergic Lesions

Pradeep K. Banerjee[1], Jouni Ihalainen[2], Timo Sarajarvi[3], Susanna Kemppainen[2], Pekka Keski-Rahkonen[4], Marko Lehtonen[4], Heikki Tanila[2]

[1]Pharmacology and Toxicology, Forest Research Institute, Jersey City, NJ, [2]Neurology, A.I. Virtanen Institute, University of Kuopio, Kuopio, Finland, [3]Neurology, University of Kuopio, Kuopio, Finland, [4]Pharmaceutical Chemistry, University of Kuopio, Kuopio, Finland

Background: The combination of donepezil (DON) and memantine (MEM) produces greater amelioration of Alzheimer's disease (AD) symptoms than DON treatment alone. We sought to elucidate mechanisms underlying that phenomenon.
Methods: Rats with cholinergic denervation of the hippocampus (fornix lesion) were treated with DON (2.5 mg/kg/day), MEM (30 mg/kg/day), or placebo in drinking water for 3 weeks, then challenged with a single i.p. dose of MEM (5 mg/kg) or DON (2.5 mg/kg). In both treatment phases, animals were subjected to an object recognition task (ORT) and microdialysis measurements of hippocampal ACh levels. Cholinergic denervation was assessed by immunohistochemistry.
Results: Fornix lesions resulted in a loss of >50% cholinergic fibers and significantly impaired ORT performance. Three weeks of MEM treatment restored ORT performance and tended to increase ACh levels, whereas DON treatment produced no significant ORT improvement. The MEM challenge following DON or vehicle treatment significantly elevated ACh release, whereas the DON challenge did not affect ACh release. Both challenges improved ORT performance.
Conclusions: Our data suggest that MEM restores recognition memory and increases hippocampal ACh release in ACh-deficient rats. This latter effect, likely resulting from NMDA receptor antagonism, in addition to the normalization of glutamatergic transmission, may underlie the benefits of MEM in DON-treated patients with AD.
Supported by Forest Laboratories, Inc.

91. Acetylcholinesterase Inhibition Ameliorates Deficits in Motivational Drive and Apathetic Behavior

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Background: Apathy is a commonly observed behavioral disturbance in numerous neurological disorders, including Alzheimer's and Parkinson's disorders as well as neuropsychiatric disorders such as schizophrenia. Apathy can be defined as a lack of motivation characterized by diminished goal-oriented behavior and self-initiated activity. We hypothesized that a commonly used stress model, chronic restraint stress (CRS), may be a useful paradigm for modeling features of apathetic behavior.
Methods: We exposed mice to daily CRS and measured behaviors related to

motivational drive and apathy. We then used FosB immunohistochemistry to help determine candidate brain regions underlying the observed behavioral changes. Based on our FosB findings and recent clinical trials, we administered the anticholinesterase phenserine and again assayed behaviors related to apathy.
Results: CRS-exposed mice showed severe deficits in motivation and initiative in a battery of behavioral tests as well as substantial accumulation of FosB in emotionally relevant brain regions including the medial septum/vertical limb of the diagonal band, a component of the cholinergic basal forebrain system. Facilitating cholinergic signaling ameliorated impairments in initiative and motivation in CRS-exposed animals.
Conclusions: Our CRS model results in behaviors that reflect a primary motivational loss and diminished emotional responsiveness, hallmarks of apathetic behavior. CRS exposure also results in FosB accumulation in cholinergic nuclei, which could potentially alter the interaction between the cholinergic system and limbic regions thought to mediate apathetic behavior. Amelioration of CRS-induced behaviors with an anticholinesterase further supports a role for the cholinergic system in mediation of apathetic behavior.
Supported by NIMH and NIA Intramural Programs

92. Longevity Gene Polymorphisms, Molecular Brain Aging Rates, and Promotion of Neurological Diseases

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Background: Mechanisms determining age of neurological disease onset are largely unknown. Molecular changes associated with normal human brain aging are robust and progressive, but their overlap with disease pathways and genetic modulation are poorly characterized.
Methods: Using a cross-cohort microarray analysis of four human brain areas, we show that neurological diseases are promoted by normal aging and that rates of promotion differentially associate with a longevity gene polymorphism (Sirt5prom2).
Results: Age-regulated gene expression changes were remarkably conserved across cohorts and included numerous developmental genes and transcriptional-regulators. Age-gated neurodegenerative and psychiatric disease-associated genes were highly overrepresented and changed almost unanimously in pro-disease directions, suggesting a genetic "program" of molecular aging that progressively promotes disease. To test this, we developed and used a biosignature-assay to assess five candidate longevity gene polymorphisms' association with molecular aging rates. Most robustly, aging was accelerated in cortex but not amygdala of subjects carrying a promoter polymorphism (prom2) of the putative longevity gene, Sirtuin 5 (+9yrs, p=0.004), in concordance with our observed area-specific decrease in Sirt5 expression. This was driven by 231 core transcripts (+24 yrs, p=0.0004), many of which were mitochondrial, including Parkinson's disease (PD) genes, PINK1 and DJ1/PARK7.
Conclusions: This promotes SIRT5prom2 as a risk factor for PD and perhaps other mitochondrial dysfunction-related diseases, through a novel mechanism, accelerated aging of mitochondrial and PD-related genes. These results demonstrate proof-of-concept for a feasible "universal mechanism" underlying age of onset across diseases and its regulation by common genetic variants and suggest new strategies for predicting, delaying, and treating neurological diseases.
Supported by NIA F30-AG030325; NIMH MH084060; University of Pittsburgh Institute of Aging

93. Selective Effects of Aging on Brain White Matter Microstructure

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Background: Reduction in gray matter volume starts relatively early and continues throughout life. In contrast, white matter volume increases through adulthood and starts to show significant decline only in the late fifties. It is currently unclear if these changes are global in nature or limited to specific white matter connections. The aim of this study was to investigate the effects of aging on brain white matter using Diffusion Tensor Imaging (DTI)-tractography.
Methods: Structural magnetic resonance images (MRI) and DTI datasets were acquired at 1.5T from 69 healthy subjects aged 22-84 years. Tract-specific Fractional Anisotropy (FA), mean/axial/radial diffusivities, and tract volume were measured in nine white matter tracts using reliable DTI-tractography protocols. We used voxel-based morphometry (VBM) and manual segmentation to determine global volumes of gray matter, white mater, cerebrospinal fluid, and intracranial space. Pearson's correlation coefficient and regression analysis were used to determine the relationship between age and tracts specific characteristics.
Results: The results showed significant effects of aging on global volumes of white matter, gray matter, and cerebrospinal fluid and selective effects of aging on structural integrity of different white matter tracts. White matter of the genu of the corpus callosum was most affected by aging, while the uncinate fasciculus, fornix, cingulum, and splenium of the corpus callosum showed relative preservation with age.
Conclusions: This study demonstrated that the frontal regions were particularly vulnerable to the effects of aging, while limbic connections were more resilient. This study was cross-sectional, therefore, additional longitudinal studies are needed to confirm our findings.
Supported by CIHR and AHFMR

94. Structural Organization of the Frontal White Matter Pathways in the Adult and Aging Brain

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Background: Understanding age-related brain changes is fundamentally important and critical to understanding age-related neuropsychiatric disorders. The frontal lobes appear to have the largest volume decline with age compared to other major lobes. We investigated the effect of aging on frontal white matter connections using diffusion tensor imaging (DTI) tractography which allows white matter tracts to be delineated *in vivo*.
Methods: We recruited 69 healthy subjects (22-84 years of age). DTI and MPRAGE datasets were obtained at 1.5T. DTI datasets were analyzed using DTI-Studio. The frontal lobes white matter was parcellated reliably into several anatomical sub-regions: medial and lateral orbitofrontal cortex

(OFC), dorsolateral prefrontal cortex (DLPFC), and medial prefrontal cortex (MPFC) using reliable tractography protocols. Tract-specific characteristics were calculated using Matlab. Pearson's correlation coefficient and different regression models were used to determine the relationship between age and structural integrity of white matter tracts.
Results: We found that OFC white matter was more vulnerable to the aging process than PFC white matter. However, their lateral/medial subdivisions followed the same developmental trajectories with aging. Fractional anisotropy in OFC white matter and in callosal tracts declined from the third decade of life, while in PFC white matter only in the fifth. The most dramatic changes in mean diffusivity occurred after the age of 60. OFC white matter, especially callosal fibers, had the largest volume reduction with age.
Conclusions: Our results suggest the selective effect of aging on frontal white matter connections. Generally, the prefrontal cortex is more preserved with aging than the orbitofrontal cortex.
Supported by CIHR and AHFMR

95. Estrogen Receptor Beta 2 and the Effective Window for Estrogen Therapy

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Background: High expression of estrogen receptor beta 2 in ovariectomized rat brain suggests that the effectiveness and the potential side effects of menopausal estrogen therapy may be regulated or mediated by this dominant negative estrogen receptor isoform. We hypothesize that the expression levels of this estrogen receptor isoform may serve as an indicator for determining the therapeutic window for menopausal estrogen therapy.
Methods: Nine month-old (an age when irregular estrous cycles occur) female Sprague Dawley rats were ovariectomized for 5 days (comparable to 4 months post-menopause of human) or 180 days (comparable 11 years post-menopause of human) before they were injected with estradiol-17β at 30ug/kg/day for 2 days. The expression of estrogen receptor beta isoforms was measured by RT-PCR and Western blot in brain and white blood cell samples.
Results: Ovariectomy increased estrogen receptor beta 2 expression in both cerebral cortex and white blood samples. Estradiol reduced estrogen receptor beta 2 expression in samples from rats ovariectomized for 5 days but not from rats ovariectomized for 180 days. There was a positive correlation between the results from white blood cells and brain samples.
Conclusions: The positive correlation between the results from white blood cell and brain samples suggest that the expression of estrogen receptor beta 2 in circulating white blood cells might be an easily accessible marker of estrogen therapy effectiveness in the brain of post-menopausal women, including those with depression.
Supported by RR17701, Alzheimer's Association IIRG, IRSP-UMC

96. The Effect of Single Prolonged Stress, a Rodent Model of Post Traumatic Stress Disorder, on Fear Conditioning, Extinction and Extinction Recall

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Background: Recent research suggests that patients with Post Traumatic Stress Disorder (PTSD) may have specific deficits in the recall of extinguished fear-conditioned associations. The single prolonged stress (SPS) paradigm is a validated animal model of PTSD that captures some of the neurobiological and neuroendocrine changes associated with the disorder, but the effects of SPS on discrete cue fear conditioning, extinction, and extinction recall have not been evaluated. This study explored the effect of SPS in three conditioning paradigms.
Methods: Rats were subjected to SPS or a control procedure. SPS rats received 2h of restraint followed by 20min forced swimming. After 15min recuperation, they were exposed to ether until anesthetized followed by a 7d quiescent period. Control rats remained in their home cages. Fear conditioning was conducted either before or following SPS and with mild (0.5mA) or strong (1mA) footshocks.
Results: SPS did not alter acquisition or expression of fear conditioned freezing in any experiment. While all rats eventually extinguished conditioned freezing, SPS altered rate of learning across trials and SPS rats exhibited an extinction recall deficit when tested 24h later. SPS had no effect on extinction or extinction recall when the larger footshock was used or when SPS was conducted after fear conditioning.
Conclusions: SPS induces changes in new aversive memory consolidation that makes fear resistant to long-term extinction, but only for 'weak' fear memories. These findings suggest SPS may be a useful model to investigate the neurobiological and pharmacological mechanisms underlying the specific processes that are altered in PTSD.
Supported by DOD

97. Alternative Splicing of Acetylcholinesterase: Relation to Stress-Induced Immobility and Anxiety in Different Mouse Strains

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Background: Alternative mRNA splicing is a means of regulating protein expression following psychological stress. Increase in the transcription of the soluble 'readthrough' variant of acetylcholinesterase (AChE), the enzyme that hydrolyzes acetylcholine (ACh), has been described following stress or exposure to AChE inhibitors. However, this effect is variable and may be dependent on mouse strain and brain region. The aim of the study was to compare 4 strains that are known to differ on their baseline level of anxiety and depression on alternative AChE mRNA splicing following injection of diisopropylfluorophosphate (DFP) or force swim stress (FST).
Methods: BALB/C, C57Bl/6, C3H/He and CD-1 mice strains were tested for baseline anxiety using double exposure to the elevated plus maze (EPM). Next mice from these strains were tested for induction of the readthrough AChE (AChE-R) using real time PCR, following 4 consecutive daily injections of DFP or 4 daily FST exposures in frontal cortex, amygdala, hippocampus and striatum.
Results: BALB/C and C3H/He mice showed more immobility than CD-1 and C57 mice on both tests. Only CD-1 mice failed to show enhanced learned

anxiety on the second EPM session. CD-1 was the only strain to show DFP-induction of AChE-R mRNA in the frontal cortex. AChE-R mRNA expression in the frontal cortex was negatively correlated with immobility in the FST regardless of strain; however, swim stress did not elicit an overall increase in AChE-R mRNA.
Conclusions: The data suggest that the potential to induce AChE-R in the frontal cortex may enhance coping with anxiety and depression.
Supported by Israel Science Foundation

98. Estrogen and Progesterone Facilitate Recall of Fear Extinction in Rats

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Background: An increasing number of studies have revealed sex differences in fear learning, implicating gonadal hormones as possible regulators of fear-related behavior. We recently began to explore the influence of gonadal hormones on fear extinction using a three-day fear conditioning paradigm in naturally cycling female rats.
Methods: In the present study, we sought to examine the role of estrogen and progesterone on the consolidation of extinction memory by systemic administration of estrogen and progesterone immediately after extinction training in one group of rats, and 4 hours post-extinction training in another group. All injections were administered to female rats while in undergoing extinction training during the metestrous phase of the estrus cycle (marked by naturally low levels of estrogen and progesterone)...
Results: Similar to previous findings in which pre-extinction administration of these hormones facilitated extinction consolidation, immediate post-extinction injection also resulted in significant extinction consolidation, as evidenced by markedly lower freezing response relative to vehicle injected rats. In contrast, injection of hormones 4 hours post-extinction training had no effect on extinction consolidation.
Conclusions: These results support our previous data indicating that extinction memory can be influenced by gonadal hormones. The current results extend to our previous data by showing that gonadal hormones specifically influence the consolidation phase of extinction learning, only when administered at short post-extinction time window.
Supported by K01MH080346

99. Electroencephalography Changes by Deep Brain Stimulation on the Orbitofrontal Cortex in an Animal Model of Obsessive Compulsive Disorder

Sandra B. Raya Santoyo[1,2], Alejandro Valdés Cruz[3], Victor Magdaleno-Madrigal[1], David Martínez Vargas[3], Rodrigo Fernández Mas[3], Salvador Almazán Alvarado[3], Fiacro Jiménez Ponce[1,4], Ángel D. Santana Vargas[1], Ylian Ramírez Tapia[5], Valentina Rojas Macías[1]

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Background: The orbitofrontal cortex (OFC) is involved in the pathogenesis of obsessive compulsive disorder (OCD). In animal models, bilateral lesion of OFC provokes a perseverative behavior in T-maze test. Low-frequency electrical stimulation (LFS) decreased perseverative behavior, and high-frequency electrical stimulation (HFS) not induces changes. The aim was to analyze the effect of HFS and LFS on electroencephalographic (EEG) activity and behavioral correlation of OCD in freely moving rats.
Methods: Six male Wistar rats were used. Bipolar electrodes were implanted in OFC. Rats were classified as follows: (a) control group, only receiving 8 OH-DPAT (1 mg/kg), (b) 8 OH-DPAT plus HFS (130 Hz), and (c) 8 OH-DPAT plus LFS (2 Hz). The electrical stimulation (100 µA, 450 µs pulses width) during 15 min was done. Further rats were assessed in T-maze test. Continual EEG activity was recorded and power band frequencies were analyzed.
Results: The EEG activity pattern induced by 8 OH-DPAT was 6.8-8.8 Hz, and 9-11.7 Hz burst was observed. The EEG activity pattern was modified by deep brain stimulation. 6.5-10.5 Hz, with burst of 8-10 Hz and 14-16 Hz with HFS were observed. 3-5 Hz and 5.8-6.8 Hz, and burst of 11-14 Hz with LFS were observed. The increase of slow frequencies power spectral was associated with perseverance behavior.
Conclusions: Our results suggest that the deep brain electrical stimulation of OFC modifies the cerebral rymths of brain areas associated with OCD.

100. The Effect of Electrical Stimulation in Orbitofrontal Cortex on Spontaneous Behavior in Rats

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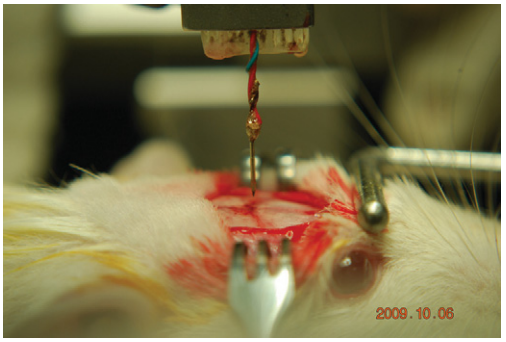
Background: Between 40 and 60% of the patients are difficult to treat in obsessive compulsive disorder (OCD), reason why FDA and WHO recognized deep brain stimulation like valid treatment in psychiatry illness. OCD T-maze model is based on "spontaneous alternation behavior" and it can be modified by 5HT1a receptor agonist (8 OH-DPAT). This substance decreases releasing of serotonin at the basal ganglia and producing a repetitive selection of the same arm in T-maze (perseveration). We suggest that orbito-frontal cortex electrical stimulation modifies perseverations in this model.
Methods: Forty eight male Wistar rats between 250 and 300 gr. have been selected by a randomized process to be part of one among six groups. Rats have been assessed in a T-maze, perseveration behavior has been quantified based on the number of the selection of same arm (1 to 7): higher value = more perseverance. We implanted bipolar electrodes in orbitofrontal cortex by stereotatic surgery the last three groups.
Results: An abnormal distribution was set by Kolmogorov-Smirnov testing variable "election".
Pre-Saline 1 (1-2), post-saline 1.5 (1-3) p=0.14 N=10; pre-8OH-DPAT 1 (1-3), post-8OH-DPAT 3.5 (1-6) p=0.01 N=10; Pre-clorimipramine 1 (1-3), post-clorimipramine 1 (1-7) p=0.10 N=10; Pre-off stimulation 1.5 (1-3), Post-off stimulation 3 (1-5) p=0.22 N=6; Pre-low stimulation 1 (1-3), post-low stimulation 1 (1-7) p=0.85, N=5; pre-high stimulation 1(1-5), post-high stimulation 4 (1-7) p=0.20 N=7.
Conclusions: Low frequency electrical stimulation decreased perseverative behavior induced by 8 OH-DPAT in same way clorimipramine group.
Sham surgery produced a partial amelioration of compulsive behavior in rats without significant differences.
High frequency electrical stimulation didn´t prevent the effect of 8-OH-DPAT.
Despite, 8- OH-DPAT is an acute model of OCD, Orbotofrontal cortex have shown a relevant role in patophysiology of this disorder. However, variation of parameters, neurochemical changes and spontaneous electrical activity should be objects from new researchs.



101. Development of a Mouse Model to Identify the Molecular Underpinnings of Extreme Behavioral Inhibition

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Background: Extreme childhood behavioral inhibition (BI) predicts the later development of psychopathology. We have developed a mouse model of extreme BI in response to exposure to a rat, a natural predator of the mouse. Having a mouse model will facilitate genetic approaches to understanding the pathophysiology of extreme BI.
Methods: Using the published rat exposure test paradigm (Yang et al, Physiol Behav 81:465-73, 2004), we exposed individual C57BL/6J mice for 10 min to an adult rat and measured the duration of BI, defined as the sum of freezing and hypervigilance.
Results: We show that the amount of BI displayed between two exposures separated by 2 days is stable both within adolescence ($r = 0.71$, $N = 48$, $p < 0.001$) and adulthood ($r = 0.91$, $N = 19$, $p < 0.001$). Importantly, the amount of BI an individual diplays in adolescence is correlated with the amount of BI that individual displays in adulthood ($r = 0.83$, $N = 12$, $p < 0.001$). BI was also related to depressive-like behaviors in the forced-swim test ($r = 0.61$, $N = 24$, $p > 0.01$). Finally, 6 mice were identified with extreme high or low levels of BI and gene chip analysis on amygdala RNA revealed 42 genes differentially expressed between the two groups.
Conclusions: These findings indicate that mouse BI is a stable trait-like characteristic. Future molecular studies characterizing the genes that are differentially expressed in relation to the amount of BI an individual displays will provide insight into novel drug targets.
Supported by R01MH40855; R01MH43454; Meriter Hospital; UW HealthEmotions Research Institute

102. PET Evaluation of Serotonin and Dopamine Transporter Occupancy Associated with Administration of SEP-225289

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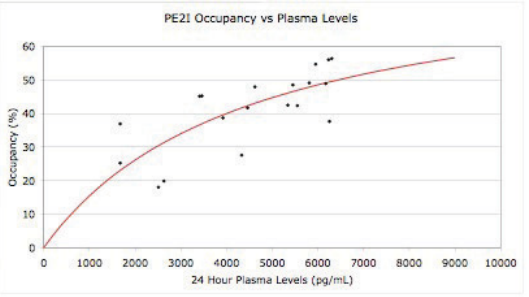
Background: SEP-225289, manufactured by Sepracor, Inc. is a monoamine reuptake inhibitor that potentially inhibits serotonin (SERT), norepinephrine, and dopamine (DAT) reuptake. This open label PET study was conducted to investigate its activity at SERT and DAT.
Methods: A single dose of SEP-225289 was administered to healthy volunteers in three sequential cohorts (8mg, n=7) (16mg, n=7) (12mg, n=5). Positron Emission Tomography (PET) imaging was performed before and ~24 hours post oral SEP-225289 administration. DAT and SERT transporter occupancy were estimated from PET using [^{11}C]PE2I[1] and [^{11}C]DASB[2], respectively. Plasma SEP-225289 concentration was assayed from blood samples collected prior to ligand injection and subjects were monitored for adverse events.
Results: Measured DAT occupancy was approximately four times greater than that of SERT. Based on a plot of DAT occupancy versus drug plasma concentration, maximum DAT occupancy was calculated as 84.94%, with an IC_{50} of 4502.13 pg/mL. Low SERT occupancy (11.8% on average) prevented similar SERT estimations. Most adverse events were mild to moderate in severity.
Conclusions: DAT and SERT occupancy increased with increasing doses of SEP-225289. SEP-225289 reaches clinically relevant DAT occupancy at the doses evaluated, and DAT occupancy exceeds that of SERT. In the dose range tested, SEP-225289 shows promise as a DAT inhibitor.



Supported by Sepracor Inc.

103. Preliminary Results of Deep Brain Stimulation in the Inferior Thalamic Peduncle as a Treatment of Obsessive Compulsive Disorder

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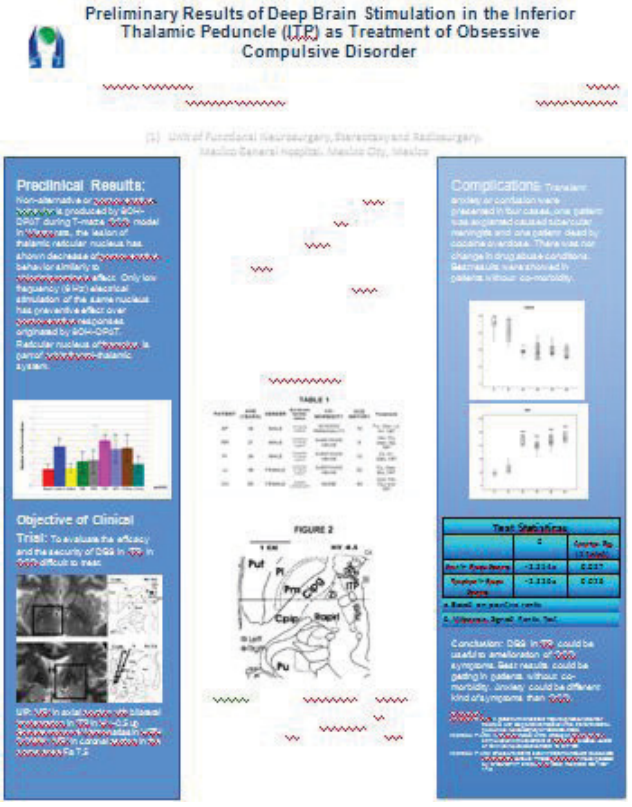
Background: Non-alternative or perseverative behavior is produced by 8OH-DPAT during T-maze OCD model in Wistar rats, the lesion of thalamic reticular nucleus has shown decrease of perseverative behavior similarly to chlorimipramine's effect. Only low frequency (6 Hz) electrical stimulation of the same nucleus has preventive effect over perseverative responses originated by 8OH-DPAT. Reticular nucleus of thamalus is part of orbitofrontal-thalamic system. Objective of trial To evaluate the efficacy and the security of DBS in ITP in OCD difficult to treat.
Methods: Six patients (1:1 male/female) with OCD (from 9 to 34 years of duration) (Table 1) were bilaterally implanted in ITP (Fig1). According to Yale-Brown Obsessive Compulsive scale (Y-BOCS) score in base line 3 patients had severe and 3 extreme OCD. They were setting at 5.0 V, 130 Hz and 450 microseconds in bipolar mode during 12 to 48 months. Y-BOCS, Global Assessment Functioning scale (GAF) and side effects check list were applied every 6 months. Drug abuse was present in three of them.
Results: Significant improve was observed in Y-BOCS and GAF score scales at 12 months of follow up.Table II. Complications - Transient anxiety or confusion were presented in four cases, one patient was explanted caused tubercular meningitis and one patient dead by cocaine overdose. There was not change in drug abuse conditions. Best results were showed in patients without co-morbidity.
Conclusions: DBS in ITP could be useful to amelioration of OCD symptoms.

Best results could be getting in patients without co-morbidity. Anxiety could be different kind of symptoms than OCD
Animal model are useful to look up the mechanism of action.
Supported by Mexican Federal Source



104. Association between Initial Treatment Modality and Two-Year Outcome in Patients with Obsessive-Compulsive Disorder

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Background: Cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) are widely accepted as first line treatments for obsessive-compulsive disorder (OCD). The aim of this study was to verify if initial treatment modality was associated with long-term outcome of OCD.
Methods: 194 consecutive, adult outpatients with DSM-IV OCD were randomized to 12-week treatment with fluoxetine (FLX-up to 80mg/day) or group cognitive-behavioral therapy (GCBT). At week 12, responders (baseline YBOCS score reduction > 35% and CGI subscore 1 or 2) to first treatment remained on the same procedure. Non-responders received uncontrolled sequential treatments between the 3rd to the 24th months, including switching and combining strategies. Baseline, 12th week and 2-year assessments were made by independent raters.
Results: At week 12, the mean decrease in YBOCS scores was 35.1% for the FLX (n=101) and 35.9% for the GCBT (n=74) group (p-value=0.7522). At 2 years follow-up, mean response rates were 54.4% for the group that received FLX (n= 40) and 54.8% for the group that received GCBT as initial treatment (n=26) (p-value=0.7034). Non-parametric ANOVA for repetitive measures showed that, after 2 years of treatment and regardless of initial treatment modality, the presence of at least one additional psychiatric diagnosis was associated with a worse outcome (p=0,0004) whereas later onset of OCD symptoms was associated with a better outcome (p=0,0071).
Conclusions: Initial treatment modality was not associated with outcome after two years. Psychiatric comorbidity predicted a poorer outcome, whereas later onset of OCD symptoms predicted good treatment response.
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105. Evidence for Unconscious, Perceptual Avoidance in Phobic Fear

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Background: Anxious patients show attentional bias reflecting automatic, rapid vigilance for threat that may contribute to symptom maintenance. Threat avoidance also characterizes anxious patients, but is thought to occur later as a secondary, conscious process, however, attentional inhibition can occur rapidly and unconsciously. Synchronized alpha event-related potentials (a-ERS) are thought to reflect attentional inhibition. The N100 ERP also reflects early attentional processes. We examined these measures in spider and snake phobics subliminally exposed to spider stimuli to explore possible early perceptual avoidance of threat cues.
Methods: Ten spider and 7 snake phobics were exposed to spider and control cues in a subliminal exposure paradigm with ERP and subjective response measures, followed by post-exposure signal detection testing to insure objective subliminality.
Results: N100 amplitude was enhanced for spider phobics responding to spider cues. A greater a-ERS effect was associated with diminished N100 amplitude and delayed latency. A greater a-ERS effect was also associated with below chance detection of spider cues, greater spider fear, and less reduction in fear after repeated exposures.
Conclusions: Alpha-ERS has been shown to reflect inhibition of attention to distracting, conscious, neutral stimuli. Our data suggest that a-ERS is also associated with rapid, unconscious inhibition of attention to salient emotional cues. The a-ERS, N100, fear and fear change data converge to suggest that avoidance of a phobic stimulus can occur unconsciously. Threat perception in phobics may reflect a balance between threat vigilance and threat avoidance, and both can occur very early in perceptual processing.

106. Exploring Cognitive Control in Working Memory in Obsessive Compulsive Disorder

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Background: Several models of Obsessive Compulsive Disorder (OCD) propose that impairments in cortical inhibitory control and sensorimotor gating yield intrusive obsessive thoughts and/ or compulsive behaviors. We therefore tested OCD patients and matched controls on the Ignore-Suppress Task, which measures ability to ignore distracting information and inhibit information in working memory.
Methods: In Ignore-condition, subjects are cued to remember red or blue words, followed by a word-set (3 red, 3 blue) and a memory probe. Suppress-condition is identical, except word-set comes before instruction-cue. Reaction time and percent errors were measured for negative probes: 1) 'dropped-

negatives'= subjects are supposed to drop words from working memory; 2) 'non-familiar negatives'= words did not appear in the word-set. Inhibitory control was calculated as difference between dropped- and non-familiar negatives.
Results: Compared to Ignore-trials, Suppress-Trials have increased reaction-time and higher error-rates in both OCD patients (n=16) and controls (n=13); dropped-negative trials have increased reaction-time and higher error-rates than non-familiar negative trials. This is consistent with prior results. However, preliminary data demonstrate that OCD patients have no deficits in inhibiting information in working memory measured by reaction-time or error-rate [Error-rate/ reaction-time: OCD=6.7/205; controls=7.7/208]; though there is a trend towards smaller error-rate on the Ignore-Task (p<.09).
Conclusions: These data contrast with that from schizophrenia patients (Smith et al, 2010), with 79% power to detect an effect size of 0.75; this task may therefore help us understand differences in pathophysiology between these highly comorbid disorders.
Supported by R24 MH080022-01

107. Brain Correlates of Escape from Shock in Virtual Reality

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Background: Prior research implicates the insular cortex in perceiving aversive stimuli, integrating physiological feedback, and generating emotional responses in coordination with the amygdala. Imaging studies show activation of the insular cortex to aversive stimuli and deactivation after cessation of threat. We adapted a virtual reality (VR) Morris Water Maze (MWM) paradigm to study active avoidance and examine brain correlates of escape from shock with whole-head magnetoencephalography (MEG). We hypothesized that activity would decrease in brain structures implicated in anxiety after participants escaped the threat of shock.
Methods: Healthy volunteers performed the VR-based equivalent of the MWM while undergoing MEG scans. In two runs, participants navigated around two virtual pools in search of an escape platform. One pool carried risk of unpredictable shocks while the other pool was safe. The MWM paradigm allowed us to examine neural correlates of escape from shock by analyzing trials in which shocks were not delivered. MEG source analyses mapped the distribution of theta (4-8Hz) activity across the brain, contrasting post-escape activity with activity in the final second before the platform was reached in both pools.
Results: Preliminary analyses (*N*=10) reveal reduced theta activity in the right insula and bilateral amygdala following successful escape from shock.
Conclusions: These data suggest anxiety-related structures show rapid reductions of theta activity after cessation of threat. Whether other regions, particularly the ventral striatum, evidence increased activity related to positive affect associated with successful escape will be addressed with further analyses of oscillatory changes in other frequency bands.
Supported by NIMH-IRP

108. Left-Right Information Transmission Assessed from Bilateral Electrodermal Activity Reflects Level of Hypnotic Experience

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Background: Recent findings indicate that interhemispheric interaction and information transition presents a general mechanism that the brain uses across different sensory modalities to increase information processing efficiency, most likely by splitting the load of processing between the two hemispheres. In this context it was proposed that interhemispheric interaction can modulate attentional capacity and selective attention mainly in conditions when attending to one stimulus needs to ignore another (e.g. Stroop task). These findings suggest a hypothesis that specific changes in selective attention and interhemispheric interactions during hypnosis could be reflected in left-right information transmission calculated from bilateral measurement.
Methods: In the present study we have performed bilateral electrodermal (EDA) measurement in 33 psychiatric outpatients (mean age 34.54) during Stroop task. The Stroop stimuli were presented in waking, during waking hypnosis and after hypnotic suggestion inducing black-white seeing.
Results: The results show that during Stroop stimuli in both hypnotic conditions the patients with higher hypnotizability (N=18) display decreased level of interhemispheric information transmission measured by pointwise transinformation (PTI) calculated between left and right EDA records. This relationship also confirms significant correlation between hypnotizability measured by Stanford scale SHSS:C and PTI during Stroop task in the period after hypnotic suggestion inducing black-white seeing (r=-0.41, p<0.01).
Conclusions: In summary, these results indicate that patients with higher hypnotizability display lower information transmission in comparison the patients with lower hypnotizability, which is likely caused by increased ability of selective inhibition and disconnection related heightened processing efficiency in susceptible individuals.
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109. Pretreatment Anterior Cingulate Activity Predicts Amygdala Attenuation in Social Phobic Placebo Responders

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Background: Previous studies have suggested that neural activity in the anterior cingulate cortex (ACC) is associated with treatment response in anxiety disordered patients. ACC, consistently reported in placebo studies, is thought to be involved in emotional control by attenuating amygdala activation. During placebo administration, amygdala attenuation appears to be important for anxiety alleviation. We aimed to investigate whether pretreatment activity in the ACC predicts amygdala decrease in placebo responsive social phobia patients.
Methods: Stress-related regional cerebral blood flow (rCBF) was measured with 15O-water positron emission tomography (PET) during public speaking before and after placebo administration in social phobia patients that responded to placebo (n=11). To investigate the functional connectivity between pretreatment ACC and amygdala, left amygdala change scores (pre-post) were extracted and used as a covariate of interest in SPM2.
Results: Higher pretreatment ACC activity (area 24) during public speech was associated with a left amygdala attenuation [(xyz) = (-8 -8 46); Z= 3.76; p corrected = .02] in placebo responders.
Conclusions: Consistent with earlier reports, ACC seems to be implicated in emotional control through downregulation of the amygdala. Because, higher ACC pretreatment activity was associated with greater placebo-induced amygdala reductions, ACC may in part regulate the clinical placebo response.
Supported by Swedish Council for Working Life and Social Research ; Swedish Research Council

110. Neurocircuitry Underlying Fear Reinstatement in Patients with Post Traumatic Stress Disorder

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Background: Post Traumatic Stress Disorder (PTSD) is a chronic disorder associated with persistent fear responses. Using a fear conditioning paradigm with fMRI, we aim to elucidate the neurocircuitry underlying heightened fear reinstatement in PTSD.
Methods: 10 PTSD patients (OEF/OIF veterans) and 10 healthy control participants took part in a 2-day fear conditioning procedure in a 3T fMRI environment. Day 1, participants underwent conditioned fear acquisition (pairing of lights with shock [CS+] or no shock [CS-]) and subsequent fear extinction. Day 2, participants had fear responses reinstated via presentation of the original US [shock] or induced via threat/trauma pictures. Each reinstatement procedure was followed by re-presentation of the CS+ and CS-.
Results: The threat/trauma pictures reinstated greater fear signal to the CS+ in the PTSD group relative to controls; specifically, higher left amygdala activation [(-20 -2 -26), 240 voxels, Z=3.92, p<.001] and heightened right insula activity [(36 -30 -16), 316 voxels, Z=3.72, p<.001]. CS- also activated the amygdala in the PTSD group [(14 -4 -18), 8 voxels, Z=2.28, p=.003], but not in healthy controls, indicating generalization of fear responding in PTSD patients only. Following shock induced reinstatement, PTSD patients did not have increased responding to CSs relative to controls.
Conclusions: These data contribute to our understanding of the neurocircuitry underlying how cues in the environment reminiscent of the original trauma can reinstate previously extinguished fear responses in PTSD patients. In addition, traumatic reminders also induced fear responding to CS- in PTSD patients only, suggesting generalization of fear responding.
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111. Stress Facilitates the Acquisition of Well-Learned Operant Behavior in a Mouse Reversal Task

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Background: Impaired cognitive flexibility is found in various neuropsychiatric disorders, where stress is a major risk factor. Reversal learning is a simple but effect tool for measuring cognitive flexibility, involving a switch in previously learned stimulus-reward contingencies. Here we examined the effects of the various stress regimens on mouse reversal learning.
Methods: C57BL/6J mice were trained on a touchscreen-based pairwise visual discrimination and then tested for reversal learning. Data were separately analyzed during early reversal (typified by prefrontal-mediated perseveration) and late reversal (striatal-mediated well-learned performance). Mice were subjected to a relatively brief stress regimen of 3 daily forced swim exposures prior to reversal (involving either short or long sessions). A separate group was stressed daily both prior to and during reversal. A control experiment examined effects of 3-day stress on learning of a simple operant response.
Results: Stressed mice were quicker to acquire late (but not early) reversal than controls. These stress effects were more robust if sessions were longer (i.e., involved more trials), or if mice were continually stressed during reversal. Stress did not affect performance on the simple operant task.
Conclusions: Current findings demonstrate that even a relatively brief stress promotes the acquisition of well-learned behavior during reversal. Given evidence this behavior is striatal-mediated our data provide further evidence that stress can promote behaviors subserved by this region, such as habit. This could have implications for understanding the effects of stress in neuropsychiatric diseases characterized by cognitive inflexibility and compulsive behaviors.
Supported by NIAAA Intramural Research Program

112. fMRI of Amygdala Reactivity to Threat Faces at Varying Intensity in Social Phobia

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Background: Generalized social anxiety disorder (GSAD) involves excessive fear in the presence of social scrutiny. This scrutiny might be perceived even at subtle levels, as GSAD patients have a negative bias in social information processing and may have a lowered sensitivity to detect threat. GSAD subjects typically show exaggerated amygdala response to 'harsh' or threatening (angry, fearful, disgusted) faces often shown at full (e.g., high) intensity. We predicted that GSAD, relative to healthy control (HC), subjects will exhibit greater amygdala reactivity to threat faces (but *not* to non-threat faces) at *both* moderate and high intensity.
Methods: Using fMRI, we measured amygdala reactivity in 16 unmedicated GSAD and 15 HC subjects while they viewed photographs of threat (angry, fearful, disgusted) and non-threat (sad, happy) expressions at low (20-30%), medium (50-60%), and high (90-100%) intensity.
Results: A priori planned two-sample t-test of signal change from anatomically-based ROIs showed that GSAD subjects had greater left amygdala reactivity to threatening faces of moderate (p<0.05) and high (p<0.03) intensity levels but not low intensity (p=0.22), compared to HCs; whole-brain voxel-wise analyses confirmed greater left amygdala reactivity in GSAD ([-21, -6, -30], t=4.07, p<0.001) at high intensity. In contrast, GSAD subjects did not differ from controls in their amygdala response to non-threatening expressions at low (p=0.86), moderate (p=0.12), and high (p=0.47) intensity.
Conclusions: These findings suggest that social phobia is associated with enhanced amygdala sensitivity to socially threatening information by responding more at less arousing signals, which may underlie the negative bias observed in GSAD patients.
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113. The Temporal Course of Conditioned Fear-Generalization in Healthy Subjects

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Background: Fear accrues to a neutral conditioned stimulus (CS) that is paired with an aversive or traumatic outcome through classical fear-conditioning. Conditioned fear responses are not limited to the original CS but can also be triggered by stimuli resembling the CS through an associative learning process called stimulus generalization. Such generalization is a promising means by which individuals with Post-traumatic Stress Disorder (PTSD) continue to experience conditioned fear in situations similar to the traumatic context. One question of interest relates to the temporal course of the generalization process.
Methods: In order to characterize fear-generalization over time, three groups of randomly assigned healthy controls were tested. The first group of subjects received acquisition training immediately followed by a stimulus generalization

test. For groups two and three the generalization test occurred 1 day and 4-6 days after acquisition training, respectively. All groups were presented with 10 quasi-randomly ordered rings of gradually increasing size with a conditioned safety cue (CS-) at one end of the size continuum and a conditioned danger cue (CS+) at the other. Objective measures of anxiety, fear-potentiated startle, and online ratings of shock-risk were collected during testing.
Results: Overall, no significant interaction was found between group type and stimulus type on physiological or behavioral measures.
Conclusions: These results suggest that in healthy controls time does not affect fear-generalization during a 1-week time period. The next phase of this work will be testing the temporal course of generalization in PTSD, with the prediction of increasing levels of generalization over time.
Supported by Intramural Research Program of the National Institute of Mental Health

114. Anxiety Modulates Hippocampal Activity during Virtual Navigation

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Background: Neuroimaging research implicates the hippocampus as an integral structure in anxiety regulation and spatial learning. To elucidate the interaction between hippocampal-dependent learning and anxiety, we used whole-head magnetoencephalography (MEG) and assessed navigation performance during a virtual-reality (VR) Morris Water Maze (MWM) task coupled with randomized presentation of shock. We hypothesized that anxiety would enhance spatial learning processes by modulating hippocampal theta (4-8Hz) activity.
Methods: MEG recordings were made as healthy volunteers (N=10) performed a VR MWM task with two sets of 20 trials in two virtual pools, one safe and one associated with threat of unpredictable shocks. During encoding, participants navigated from random starting locations to a visible platform at a fixed location. During retrieval, participants navigated to a submerged platform, invisible to the participant, but positioned in the same location as during the encoding phase. Distal cues on surrounding walls could be used to navigate efficiently to the hidden platform. Navigation performance measures included angular heading error and path length to the platform. MEG source analyses focused on the distribution of theta (4-8Hz) activity and modulation of medial temporal cortical activity across threat and safe conditions during navigation to the visible and hidden platforms.
Results: Preliminary analysis reveals superior navigation performance to the hidden platform under threat of shock. Source analyses revealed increased theta activity in bilateral hippocampus and parahippocampal cortices during threat compared to safe conditions.
Conclusions: Improved navigation performance and increased hippocampal/parahippocampal theta activity under aversive conditions suggests anxiety directly modulates hippocampal mechanisms of spatial learning.
Supported by Intramural Research Program of the National Institute of Mental Health

115. Electrophysiological Correlates of Attentional Processing in Obsessive-Compulsive Disorder

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Background: Event related potentials (ERP) components P300, mismatch negativity (MMN) and P50 reflects in some degree attentional processes impaired in obsessive-compulsive disorder (OCD) and other neuropsychiatric syndromes. Reported ERP findings are P300 decreased amplitude and shortened latency, MMN reduced in attentional-independent processes and, sensory gating observed in impaired supression of P50. Several reports have used ERP measurements as individual neurophysiological correlates of cognitive disruptions. Whereas measured in conjunction they may provide a distinctive profile apart from similar disturbances as well in healthy population.
The present research is a pilot study aimed to find tendencies to formulate an ERP profile with a three fold evaluation of dependent and independent attentional processes in OCD patients.
Methods: Participants were 7 male and 3 female OCD patients (mean age =36.02 years old; d.s. = 11.8) and 10 age and sex matched with healthy controls. ERP were recorded at 10-20 international system electrode positions refered to shortcuted ear lobes.
Results: The OCD group showed decreased P300 amplitude, larger negativity in MMN and higher supression ratios in P50. A different pattern were found in control subjects with larger P300 amplitude, minor MMN effect and lower P50 supression.
Conclusions: Collectively ERP measures showed abnormal variations in OCD patients. These differences are congruent with the reported hypothesis of higher cortical activity reflected in early stages of non directed attentional processing (P50 and MMN) and disruptions in the later selective-directed attention (P300). A larger sample is necessary to support this prelimiray profile.

116. Friend or Foe? Neural Correlates of Reciprocity and Defection in the Trust Game in Social Phobia

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Background: Social neuroeconomics seeks to uncover brain mechanisms that explain the formation and maintenance of social bonds, and has shown that fair/equitable outcomes activate reward-responsive regions including ventral striatum (vSTR), while unfair outcomes provoke insula, an area implicated in aversion. Disturbances in these neural regions could underlie the social dysfunction observed generalized social anxiety disorder (GSAD).
Methods: Using event-related fMRI, we measured brain activity in 40 GSAD participants and 36 healthy controls (HCs) during an iterative Trust Game. In each round, participants decided whether to invest in a fictive trustee partner whose 'reputation' for reciprocity varied and was unknown to the participant prior to scanning. fMRI data were analyzed in an SPM5 random-effects model with whole-brain significance set at voxel-level $p<0.001$ uncorrected and cluster-level $p<0.05$ corrected.
Results: HCs exhibited robust activations in bilateral vSTR (Right:[20,12,-10],Z=4.88;Left:[-26,8,-8], Z=4.48) in response to partner reciprocity; a similar response was observed in the GSAD group (Right:[14,12,-8],Z=6.39;Left:[-12,12,-8], Z=6.51). Follow-up analysis revealed partner-type

significantly modulated vSTR responses in HCs, with enhanced activation to partners who have consistently returned the investment (e.g., earned a reputation for reciprocity). In contrast, GSAD participants showed no differential vSTR response across partner types. Partners with a reputation for defection evoked greater reactivity in right insula ([34,10,-6],Z=3.2) in the GSAD group than the HC group.
Conclusions: In probing the dynamic nature of social interactions, we have identified a novel brain mechanism (via vSTR) that may play a role in signaling social reciprocity and may differ in its function in patients with social phobia.
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117. Relation between Psychiatric Symptoms and Cortisol in the Process of Surgery Recovery

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Background: The aim of this study was to determine whether there was a relation between cortisol level and psychiatric symptoms in the process of Surgery Recovery.
Methods: The sample was composed of 42 patients (age range: 25-70) from the Surgery Department, Infanta Cristina University Hospital in Badajoz. Patients who presented impaired cognitive functioning were excluded from the study. Prior to surgical intervention (48 to 72 hours), patients were administered the Symptom Check List 90-Revised (SCL 90-R). Salivary cortisol were measured 24 hours before surgery. Following surgical intervention, recovery was coded as "good" or "poor" accordingly to Moix et al.'s criteria (1995). The inpatients' dietary intake, resting and sleeping hours as well as fever, perceived pain and related surgery complications were daily registered and controlled for.
Results: The patients with high score in anxiety and cortisol show worse recovery from surgery ($F = 4.96$, $p = 0.042$).
Conclusions: The results of this study indicate that preoperative anxiety and high levels of cortisol may have a critical rol in postoperatory recovery. Taking these data into account, it seems necessary to assess psychopathology on a regular basis in all the patients waiting for surgically interventions.

118. Role of BDNF val66Met Polymorphism on the Association Between Physical Activity and Incident Dementia

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Background: Increased physical activity may have beneficial effects on cognitive outcomes; a role of brain-derived neurotrophic factor (BDNF) has been suggested in animal models but not yet tested in humans. This study investigated modification by BDNF val66met polymorphism of the association between physical activity, incident dementia.
Methods: Of 732 community elders, 107 had dementia at baseline, and 518 (83%) of the remainder were followed over 2.4 years. Cognitive impairment were defined from Mini-Mental State Examination scores. Self-reported level of physical activity was recorded on a 4-point scale. BDNF val66met and apolipoprotein E genotypes were ascertained. Covariates included age, sex, education, depression, vascular risk factors, and instrumental activities of daily living.
Results: Baseline lower physical activity was significantly associated with incident dementia as well as with baseline dementia and cognitive impairment and incident cognitive decline. BDNF val66met polymorphism itself was not associated with any cognitive outcome. However, the strength of association between lower activity and all cognitive outcomes increased incrementally with the number of met alleles, and was strongest in those with the met/met genotype. BDNF x activity interaction terms were stronger for prospective outcomes (incident dementia, cognitive decline) compared to cross-sectional outcomes (prevalent dementia, cognitive impairment no dementia).
Conclusions: This study supports a previously suggested neurobiological basis for the effects of physical activity on dementia involving the BDNF system since the met allele is recognised to be associated with lower activity-dependent secretion of BDNF.

119. Altered Cortical Development and Working Memory Deficits After Early Life Stress

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Background: Early adverse experience plays an important role in psychopathology by altering memory and motivational processes. These effects typically manifest during adolescence, in parallel with the later-developing prefrontal cortex (PFC). The PFC mediates motivational salience and decision-making, partially through its connectivity with the nucleus accumbens (NAc). While it is likely that the PFC is involved in delayed effects of early life stress, little is known about how environmental events modulate its development.
Methods: From postnatal day (P)2-20, rats received maternal separation stress (MS) or facility rearing (CON). Brains from MS (n=6/age) and CON (n=6/age) males were taken at three ages: juvenile (P25), adolescent (P40), and adult (P100). Five days previously, rats received microinjections of retrograde tracer into the NAc to identify PFC-NAc projections. The prelimbic PFC (plPFC) was analyzed with immunohistochemistry and Western blot for expression of the D2 dopamine receptor (D2R) and parvalbumin (a marker of fast-spiking interneurons). Additionally, we assessed D2R distribution on traced or PVB-positive neurons. A separate set of rats (n=8) was tested at P50 for working memory performance on the win-shift task.
Results: During adolescence, D2R were transiently over-expressed on plPFC-NAc projection neurons in CON ($p<0.01$) but not MS animals. Moreover, MS adolescents had reduced PVB-positive interneurons, indicated by immunohistochemistry ($p<0.01$) and Westerns ($p<0.05$). In late adolescence, MS rats made more errors in the win-shift task compared with CON rats ($p<0.01$).
Conclusions: The effects we report here reveal specific cortical changes caused by early life stress that could help explain delayed vulnerability to psychopathology.
Supported by Shine Initiative, NARSAD

120. Developmental Trajectories of Transcripts Regulating GABA Neurotransmission in Monkey Prefrontal Cortex

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Background: The development of working memory, a core cognitive deficit in schizophrenia, parallels the protracted maturation of prefrontal cortex (PFC) circuitry in monkeys and humans. Given evidence that schizophrenia is a neurodevelopmental disorder, studying the developmental trajectories of transcripts involved in GABA synthesis, reuptake and postsynaptic receptors may provide insight into the illness pathogenesis. Glutamic acid decarboxylase 67 (GAD67) synthesizes most cortical GABA, while GAD65 contributes to GABA synthesis during periods of repetitive firing. PFC levels of GAD67 mRNA, but not GAD65 mRNA, are decreased in schizophrenia. GABA acts at postsynaptic receptors containing $\alpha 1$ subunits and this action is terminated

via the GABA membrane transporter (GAT1). Expression of mRNAs for GABA receptor subunits and GAT1 are altered in schizophrenia. Here we define postnatal developmental trajectories of these pre- and postsynaptic GABAergic mRNAs in monkey PFC.
Methods: Frontal pole (BA 10) tissue from 45 rhesus monkeys was used for quantitative real-time RT-PCR. We quantified GAD67, GAD65, GAT1, and $GABA_A$ α1 receptor subunit mRNAs, using β-actin and cyclophilin-A as control genes.
Results: Expression of all transcripts increased between 7 days to 42 months of age (GAD67 +25%, GAD65 +97%, GAT1 +56% and $GABA_A$ α1 +99%). Each transcript exhibited a distinctive developmental trajectory.
Conclusions: These data indicate that transcripts regulating GABA neurotransmission have unique developmental trajectories, suggesting that differences may exist in the timing of their vulnerability to pathogenetic events in schizophrenia. Future studies will compare these trajectories between affected and unaffected cell types in schizophrenia.
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121. Default Mode Network's Activity in Social Interaction: Increase or Decrease?

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Background: Recent neuroimaging studies most often attempt to explore the functional neuroanatomy of social cognition by examining brain regions that subserve the understanding of psychological characteristics of other people, whilst brain correlates of socially-situated interactions have never been studied. To explore the brain bases of social interactions, we have conducted a fMRI study using a simple imitation paradigm that doesn't require mentalizing abilities.
Methods: The fMRI and behaviour of 25 participants were recorded while they imitated the experimenter's hand movements or were imitated by the experimenter. A double video system adapted to the MRI environment allowed participant and experimenter to see each other's movements. Two different imitation conditions were proposed: a spontaneous condition leading to reciprocal turn-taking between roles of model and imitator (S: subject imitates or proposes hand movements to be imitated, at will) and induced condition (I: subject imitates or proposes movements when requested).
Results: A significant decrease of activity was found in default mode network (DMN) areas when the participant was imitated compared to the imitation condition, regardless of spontaneous or induced conditions. This result cannot be explained by a greater activity in dorsal-lateral prefrontal areas, known from previous studies to be anti-correlated with DMN.
Conclusions: Considering the important role of 'be imitated' in originating a feeling of shared understanding during dyadic interaction, we hypothesize that the maximum decrease of DMN activity in this condition reflects the 'external engagement' required by 'sharing' with another. We suggest that genuine interaction tasks do not involve self-reference but rather self-oblivion.
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122. Event Related Coherence of Healthy Subjects upon Application of an Auditory Oddball Paradigm

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Background: Previous studies on local oscillatory dynamics showed that the major operating rhythms of P300 are mainly the delta and theta oscillations. However, the analysis of long-distance coherence upon application of an auditory oddball paradigm was not yet performed. In this study, the long-distance intra-hemispheric event related coherence (auditory oddball paradigm) and evoked coherence (simple sound) of healthy subjects were compared in order to evaluate the effects of cognitive tasks on the long-distance coherences of healthy subjects.
Methods: 17 healthy subjects (8 female, 9 male) were included in the study. The coherence was analyzed for delta (1-3.5 Hz), theta (4-7.5 Hz) and alpha (8-13 Hz) frequency ranges for (F_{3}-P_3, F_4-P_4, F_3-T_7, F_4-T_8, F_3-O_1, F_4-O_2) electrode pairs.
Results: The *target* coherence values were higher than the *non-target* and simple auditory stimulation coherence values. This difference is significant for the delta coherence for both hemispheres ($p<0.05$) and it was significant for theta coherences over the left hemisphere ($p<0.05$). It was not significant for the alpha coherence. The highest coherences were found at fronto-temporal locations for all frequency bands (delta, theta, alpha) ($p<0.05$). Furthermore, fronto-parietal coherences were higher than the fronto-occipital coherences for all frequency bands (delta, theta, alpha) ($p<0.05$).
Conclusions: These results show that the fronto-temporal and fronto-parietal connections are most relevant for the identification of the target signal triggering focused attention and increase working memory. These results may, in turn, serve in future to accomplish a more differentiated use for analysis in neuropsychiatric patients.

123. Early Life Stress Due to Maltreatment in Childhood Modulates Reward Processing During an Inhibitory Control Task: An Antisaccade Study

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Background: Early life stress (ES) has been associated with impulsive behaviour and inhibitory deficits. Independently, perturbations in the neural substrates subserving reward processing have been noted. However, little is known about the interaction between reward processing and cognitive control in youth who experienced ES.
Methods: Here, we examined the impact of ES on reward processing using a mixed saccade task. Sixteen adopted children (9 females, 11.4 years ± 2.0) with a history of maltreatment were compared to 36 healthy youth (17 females, 13.2 years ± 2.7) without such history and who resided with their biological parents. Participants executed randomly mixed prosaccades (toward a target) and antisaccades (opposite direction to the target). During the trials, cues indicated not only the type of saccade to be performed but also whether participants could win or lose money depending on the correctness of their eye movement (incentive condition). No incentive trials regardless of saccade accuracy were interspersed with incentive trials to serve as baseline.
Results: Adopted youth improved prosaccade but not antisaccade latencies with incentive relative to no incentive trials. By comparison, healthy controls improved antisaccade but not prosaccade error rates with incentive. Moreover, overall latencies for ES youth were slower than for controls.
Conclusions: The present data suggest that ES affects reward processing abilities when strong levels of inhibitory control are required but are facilitated

when prepotent saccades have to be executed. However, overall saccade latency is slowed after ES and suggests impact on the ocular response system.
Supported by intramural program of NIMH

124. Executive Attention Network Impairment Children with Chromosome 22q11.2 Deletion

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Background: Chromosome 22q11.2 deletion syndrome (22q11.2DS) is a genetic model of schizophrenia. Several small studies have discovered executive attentional network impairments in 22q11.2DS which are similar to impairments related the development of schizophrenia. We hypothesized that such impairments in the executive control of attention in 22q11.2DS are related to age.
Methods: Forty-eight typically developing (TD) and 66 children with chromosome 22q11.2 deletion syndrome were tested the attention networks task (ANT). We used linear mixed modeling to account for intersubject variability, age, handedness, location tested, and gender on performance for all experimental (cue X flanker) conditions and their two-level interactions.
Results: Children with 22q11.2DS showed relative executive index impairment (t(df) = -2.20 (94.8), p = 0.30) but not orienting or alerting network index impairments. In factorial analysis, the overall effect of 22q11.2DS was a 15% adjusted reaction time (RT; reaction time/accuracy) cost with an additional 7% cost on the incongruent flanking condition (p<0.001). Across groups, age was the dominant predictor of overall performance 0.6% reaction time (RT) benefit per month, e.g. a 56% RT benefit for a 14 year-old versus a 7 year-old (p<0.001). While all participants improved with age on the flanking condition, age did not interact with the presence of 22q11.2DS.
Conclusions: Children with 22q11.2DS demonstrated age-related impairment in the executive control of attention. Further investigation may reveal that there are different developmental trajectories of executive attentional function related to the development of schizophrenia in 22q11.2DS.
Supported by R01HD42974; UL1 RR024146

125. Serotonergic Neurotransmission in ADHD: Availability of Tryptophan Influences Attentional Performance in Children and Adolescents

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Background: Changes in serotonergic (5-HT) neurotransmission have been shown to be associated with altered attention and memory processes. As attention-deficit/hyperactivity-disorder (ADHD) is associated with impaired working memory and attention, the present investigation focused on the effects of a diminished central nervous 5-HT turnover on attentional performance in children and adolescents with ADHD.
Methods: We recruited 22 male patients with ADHD (aged 9-15 yrs.) who received the rapid tryptophan depletion (RTD) procedure Moja-De on one day within an amino acid drink lacking tryptophan (TRP-). On a second day they ingested a TRP balanced placebo. TRP-/TRP+ were administered in a randomized double-blind within-subject crossover design (TRP+). Lapses of attention (LA) were assessed within the test-battery for attentional performance under TRP-/TRP+ at 120 (T1), 220 (T2) and 300 (T3) minutes after intake of TRP-/TRP+.
Results: There was a significant main effect for the treatment factor at T1 as there were more LA observed after the intake of TRP+ compared with the TRP- condition. For T2/T3 there were no such effects for TRP-/TRP+.
Conclusions: We are the first to report altered attentional processes after manipulation of the central nervous 5-HT turnover on the precursor level in children and adolescents with ADHD. The present findings could be influenced by interactions of 5-HT with other neurochemical processes such as changes in dopaminergic neurotransmission, which should be subject of future investigations.
Supported by Dr. August Scheidel Foundation

126. Common Genetic Factors Influence Intelligence and Cortical Surface Area

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Background: Consistent, but weak, correlation between IQ and brain structure has been shown, with the suggestion that up to 10% of the variation in intelligence could be explained by brain volume [1,2]. The correlation was suggested to be of genetic origin [3]. Here, we test for pleiotropy between IQ and two genetically independent measurements of brain anatomy, cortical thickness and surface area.
Methods: High-resolution T1-weighted MRI scans were acquired from 632 subjects from randomly selected extended pedigrees. Surface-based methods were used to derive measures of gray matter thickness and cortical surface area as described in [4,5]. Full-scale IQ was assessed using WASI on all subjects.
Results: IQ was phenotypically more significantly correlated with global brain surface area (0.194, p=5.3e-5) than with average cortical thickness (0.055, p=2.6e-1). Regionally, the correlation was phenotypically and genetically more significant for the surface area of frontal regions, notably for regions in the middle and inferior frontal and orbitofrontal gyrus, as well in the cingulate.
Conclusions: Cortical thickness was not significantly correlated with IQ for any brain region, even using liberal significance levels.
Supported by R01-MH0708143

127. Divergent Regulation of Pro-BDNF and Mature BDNF Expression during Development in Human Prefrontal Cortex

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Background: Mature BDNF (mBDNF) and its precursor Pro-BDNF exert opposing influences on neuronal survival and plasticity. The expression of Pro-BDNF relative to that of mBDNF undergoes dynamic changes during development in rodent brain but has not been elucidated in developing human

cortex. This study compared the expression of Pro-BDNF and mBDNF during development in human prefrontal cortex.
Methods: Pro-BDNF and mBDNF protein levels were measured by Western blotting in postmortem dorsolateral prefrontal cortex (DLPFC) of 39 subjects without neurological or psychiatric disease ranging in age from 18 gestational weeks to 25 years. Samples were batched a priori into fetal, infant, 1-5 year, 6-10 year, 11-15 year, and 21-25 year age groups for group comparisons by ANOVA. The relationships of Pro-BDNF and mBDNF to age and BDNF transcript expression were investigated by regression analysis.
Results: Pro-BDNF and mBDNF expression patterns differed markedly during fetal and early postnatal development. mBDNF expression was lowest in the fetal group and increased five-fold between midgestation and infancy and a further seven-fold by adolescence, whereas Pro-BDNF expression in the fetal group was 2.5-fold greater than that of infant levels and comparable to that of adolescent levels.
Conclusions: Pro-BDNF and mBDNF have markedly divergent expression patterns which are reflected by a dramatic increase in the expression of mBDNF relative to that of Pro-BDNF during fetal to early postnatal development in human DLPFC. These findings suggest that increased efficiency of Pro-BDNF processing coincides with the profound expansion of synaptic density which occurs in early frontocortical development.
Supported by Foundation of Hope

128. Higher 5-HT(2A) Cortical Receptor Binding in Brains of Youth Suicide

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Background: Higher 5-hydroxytryptamine 2A ($5\text{-}HT_{2A}$) receptor binding has been reported in the postmortem brains of both adult and teenage suicide victims. It is also known that $5\text{-}HT_{2A}$ receptor binding declines with age. In this study we analyze the serotonin binding levels as a function of suicide, age at death and brain region in postmortem brains from young subjects.
Methods: $5\text{-}HT_{2A}$, $5\text{-}HT_{1A}$ receptor and serotonin transporter binding was quantified by autoradiography in 8 suicides and 12 sudden death subjects, all males, between the age of 13 and 25, in brain regions BA 9, 11, 12, 20, 21, 22, 32, 36, 45, 46, 47. 6 out of 8 suicides had a diagnosis of Major Depressive Disorder (MDD). A mixed effect regression model was used to test binding as a function of brain region, age and cause of death.
Results: Suicides had higher $5\text{-}HT_{2A}$ receptor binding (p=.0082) than sudden death controls in all brain regions, binding levels declined with age (p=.0382) in both suicide and control brains, and were significantly different by brain region (p<.0001), with the highest binding in areas 11 and 47, and the lowest in area 45. Binding levels of the $5\text{-}HT_{1A}$ receptor and the serotonin transporter differed significantly by brain region (p<.0001), but not by age or cause of death.
Conclusions: The difference in brain $5\text{-}HT_{2A}$ receptor binding in youth suicide compared with sudden death controls is widespread throughout the brain regions and persists from adolescence into young adulthood despite the decline in binding levels with age.
Supported by MH074068, MH40210, MH47097, and MH46745

129. An Initial Delineation of Growth Rates of the Corpus Callosum in Attention-Deficit/Hyperactivity Disorder

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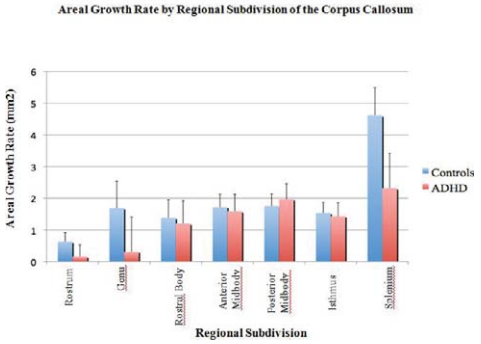
Background: Structural differences of the corpus callosum have been consistently implicated in ADHD, but it is unclear whether these differences are age dependent. In this pilot cross-sectional study, we determined regional growth rates of the corpus callosum in children with and without ADHD.
Methods: 100 children (62 male; mean age 11 yrs, SD 3.5) with combined type ADHD were compared with 50 typically developing children (31 male; mean age 10.5, SD 4). 1.5T T1-weighted SPGR axial images were obtained, registered into stereotaxic space, corrected for nonuniformity artifacts and segmented. Areas of the seven callosal subdivisions as defined by Witelson (1989) were determined from the midsagittal slice. We tested for effects of diagnosis and interaction between diagnosis and age on callosal surface area, controlling for total brain volume.
Results: There were no significant diagnostic differences in total callosal area. However, we found slower callosal growth in the splenium in ADHD (ADHD rate 2.31mm2/year SEM 1.11; controls rate 4.61mm2/year SEM 0.88; t=2.1, p=0.04). A non-significant trend to slower growth was found in anterior regions (genu: ADHD rate .31 mm2/year SEM 1.1; controls rate 1.68 mm2/year SEM .86; t=1.3, p=.22).
Conclusions: Evidence of slower growth in the posterior corpus callosum in ADHD can inform our understanding of anomalous interhemispheric processing reported in the disorder. We intend to refine the delineation of callosal growth trajectories using longitudinal data.



Supported by NIMH

130. Genetic and Environmental Contributions to Neonatal Brain Structure: A Twin Study

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Background: Twin studies have found that global brain volumes, including total intracranial volume (ICV), total gray matter, and total white matter volumes are highly heritable in adults and older children. Very little is known about genetic and environmental contributions to brain structure in very

young children and whether these contributions change over the course of development.
Methods: We performed structural imaging on a 3T MR scanner of 217 neonatal twins, 41 same-sex monozygotic, 50 same-sex dizygotic pairs, and 35 "single" twins - neonates with brain scans unavailable for their co-twins. Tissue segmentation and parcellation was performed, and structural equation modeling was used to estimate additive genetic, common environmental, and unique environmental effects on brain structure.
Results: Heritability of intracranial volume (0.73) and total white matter volume (0.85) was high and similar to that described in older children and adults; the heritability of total gray matter (0.56) was somewhat lower. Heritability of lateral ventricle volume was high (0.71), while the heritability of cerebellar volume was low (0.17).
Conclusions: Comparison with previous twin studies in older children and adults reveal three general patterns of how heritability can change during postnatal brain development: 1) for global white matter volumes, heritability is comparable to reported heritability in adults, 2) for global gray matter volume and cerebellar volume, heritability increases with age, and 3) for lateral ventricle volume, heritability decreases with age. More detailed studies of the changes in the relative genetic and environmental effects on brain structure throughout early childhood development are needed.
Supported by RO1MH070890

131. Neuro-Functional Networks Supporting Cross-Sensory Emotion Processing in Teens with Autism Spectrum Disorder

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Background: The processing of social information involves a network of distributed brain regions, many of which appear to be aberrant in ASD. Because information from the different senses is typically complimentary, cross-sensory integration of sensory input provides information about the environment that is unobtainable from any one sense in isolation. Failure to integrate multi-sensory social-emotional information could be expected to result in considerable social deficit. Our objective, therefore, was to investigate the neural circuitry underlying the processing of socially important, affective multimodal cues in high functioning teenage boys with ASD.
Methods: High functioning teenage males with autism (13-19 years old) and matched controls participated in the fMRI study. Individually thresholded emotional face stimuli (% of maximal) were used in a cross-sensory task that involved the matching of an emotion face and voice combination to an emotion label. This design permitted a test of how successful integration can facilitate the processing of emotion in difficult to detect situations.
Results: : Preliminary results on 12 subjects with autism and 16 controls identify greater recruitment of the insula, superior temporal and parietal cortices in typically developing teens. In contrast, teens with autism show greater recruitment of the superior prefrontal cortex.
Conclusions: These results suggest, when typically developing teens are processing cross-sensory emotion cues they recruit areas involved in face and emotion processing, integration of emotional state and physical responses to arousal and social relevance. In comparison, teens with autism show greater engagement of our regions associated with working memory and problem solving.
Supported by McMaster University, Psychiatry and Behavioural Neuroscience

132. Neurocognition and Temperament in Depersonalization Disorder

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Background: Depersonalization Disorder (DPD) is characterized by a persistent or recurrent feeling of being detached from one's mental processes or body, and a sense of unfamiliarity/unreality and hypo-emotionality, but with intact reality testing. We explored the neurocognitive and temperament profile of DPD patients to better understand their underlying neurobiology and the neural basis of dissociation.
Methods: 19 DPD patients and 22 matched healthy controls were given a comprehensive neuropsychological battery (CANTAB), the Iowa Gambling Task, a time perception task, and questionnaires of impulsivity, temperament, emotion, and frontal behavior (measures orbitofrontal cortex (OFC) dysfunction).
Results: Compared to healthy controls, DPD patients performed significantly better on the Intra-Extra Dimensional Set Shift task (IED) and no worse on any other cognitive task, except for having a significantly faster subjective sense of time, which positively correlated with their attentional impulsivity. DPD patients experienced more childhood trauma, negative emotions, and dissociation, and were more impulsive, neurotic, and harm avoidant and less extraverted, agreeable, conscientiousness, and self-directed. They also had more frontal behaviors which positively correlated with their emotionality, neuroticism, and childhood trauma.
Conclusions: Dorsolateral prefrontal cortex (DLPFC) hyperactivation may explain DPD patients' enhanced IED performance, a task sensitive to DLPFC function. Memory suppression and emotional regulation has been associated with increased DLPFC and reduced limbic activation. DLFC inhibition of limbic structures may mediate DPD patients' ability to dissociate and their hypo-emotionality. However, OFC dysfunction appears to be related to their other problems, such as their time perception deficits, negative emotions, neuroticism, impulsivity, and childhood trauma.

133. The Relationship between Amygdala Activation to Emotional Faces and Anxiety Symptoms in Adolescents with Autism Spectrum Disorders

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Background: Individuals with autism spectrum disorders (ASD) have high rates of anxiety symptoms. However, no known study has examined the relationship between anxiety symptoms and brain function in ASD. Since the amygdala is a structure most associated with anxiety, we hypothesized that amygdala activity during the viewing of threatening stimuli would be related to anxiety symptoms in individuals with ASD.
Methods: Twenty-eight adolescents with ASD and 25 healthy controls viewed briefly presented (250ms) emotional (fearful, happy, sad) and neutral faces while completing a gender identification task during fMRI scanning. Participants also completed a scale that assesses symptoms of generalized and social anxiety.
Results: We used a small volume correction approach $p<.05$ on the bilateral amygdala region of interest to test the relation between amygdala activity and anxiety scores. Though data collection is ongoing, initial results with the current sample indicated there was a significant interaction of bilateral amygdala activation between group (ASD, control) and anxiety symptoms for the fearful

vs. neutral faces contrast $F(2,50)=4.18$, $p=.02$. This interaction was driven by a significant negative association between anxiety scores and bilateral amygdala activity when anxiety scores were entered as a regressor in SPM within the ASD group, $t(26)=-3.80$, $p=.03$. These effects were specific to threatening stimuli (fearful faces), since there was no association in the ASD group between anxiety scores and amygdala activity in the sad or happy vs. neutral contrasts.
Conclusions: These results indicate that degree of anxiety symptoms in ASD are associated with less amygdala reactivity to fearful faces.
Supported by Autism Speaks;NIMH U19 HD35482;MH066496

134. Predicting the Effect of Methylphenidate Hydrochloride in Children with ADHD Using Multi-Channel NIRS

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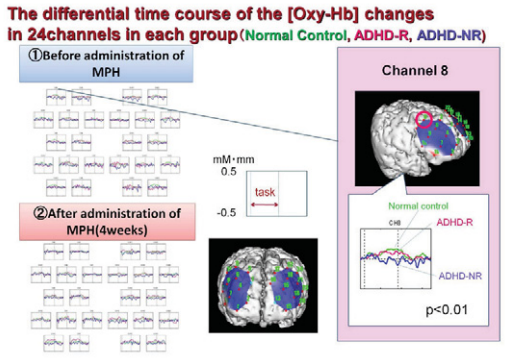
Background: The use of stimulant drugs for attention-deficit/hyperactivity disorder (ADHD) has raised questions about the possibility of over-treatment. It is necessary to develop biologically-based criteria to adjust treatment appropriately. Near-infrared spectroscopy (NIRS) is a noninvasive neuroimaging method that can measure relative changes in the concentration of oxygenated hemoglobin ([Oxy-Hb]) in cortical tissue in natural settings. The stop signal task is suitable for detecting the dysfunction of response inhibition in ADHD. The aims of our study were to examine the bilateral prefrontal activation associated with response inhibition by using multi-channel NIRS in children with ADHD, and to develop a neurophysiological index which predicts the effect of continuous administration of methylphenidate hydrochloride (MPH) on the cognitive function evaluated by Das-Naglieri Cognitive Assssment System (DN-CAS).
Methods: Participants were 14 children with ADHD and 20 typically developing children. We defined the children with ADHD whose total score or subscale score of DN-CAS was improved after administration of MPH as responder (ADHD-R) and the children with ADHD whose score was not improved as non-responder (ADHD-NR).
Results: ADHD-NR showed the lower [Oxy-Hb] increase than ADHD-R and typically developing children during the activation task in right dorsolateral prefrontal cortex (DLPFC) ($p<0.01$).
Conclusions: The activation of [Oxy-Hb] in right DLPFC represented the difference of the frontal lobe function between responder and non-responder before administration of MPH. These results suggest that NIRS might be potentially useful as a neurophysiological index which predicts the effect of MPH in children with ADHD.



Supported by H20-kokoro-001,2008-MeijiYasuda

135. Brain Activities in Depressed Adolescents During a Working Memory Task: Pre- and Post-Fluoxetine Treatment

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Background: Decreased concentration and memory are common symptoms of depression. Depressed adults had been found to have greater recruitment of prefrontal cortex and anterior cingulate cortex during working memory tasks. Although major depressive disorder is prevalent among youths, little imaging research has been done in this population. The purpose of this study was to evaluate brain activities of treatment-naïve depressed adolescents compared to normal controls, and to determine changes in brain activity following 8 weeks of treatment of fluoxetine.
Methods: Fifteen depressed adolescents and and 14 normal controls (11 to 18 years) were evaluated. Depression severity was assessed by the Children's Depression Rating Scale-Revised (CDRS-R). Both depressed and normal adolescents were scanned twice using a Philips 3T MR scanner at baseline and week 8. Depressed adolescents received 8 weeks of fluoxetine treatment after the baseline scan. Blood oxygenation-level dependent functional images were acquired using gradient-echo echo planar imaging sequence when adolescents were performing a working memory task.
Results: At baseline, depressed youths had greater positive signal change in medial prefrontal cortex (PFC), less negative signal change in right inferior parietal cortex and greater negative signal change in the posterior cingulate, right lateral occipital, parietal and superior frontal cortex. After 8 weeks of fluoxetine treatment, depressed adolescents had decreased PFC activation compared to baseline activation.
Conclusions: Similar to adults, depressed adolescents had increased prefrontal cortex recruitment during working memory tasks compared to healthy controls. After 8 weeks of fluoxetine treatment, depressed adolescents required less PFC involvement which may indicate increased efficacy.
Supported by The Klingenstein Third Generation Foundation

136. Relationship between Novelty Change Detection and Autistic Traits in Adolescents with Autism

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Background: The neural correlates of repetitive and unusual restricted behaviors in autism remain poorly understood. One dimension of these behaviors, described as 'resistance to change', may be related to atypical processing of salient and novel information. This can be tested at sensory and neural levels. Our aims were (i) to investigate the neural correlates of change detection and attention deficit in adolescents with autism using neuroimaging and (ii) to examine the association between brain activations to novel sounds and clinical measures.
Methods: Ten adolescents with autism were imaged on a GE 3T MRI scanner (TR: 2000 ms; TE: 27ms; FOV: 256; image matrix: 64 × 64; Flip angle 60; Voxel size: 4 ×4 × 3.8 mm; 34 axial slices). Subjects passively listened to novel sounds embeded in a series of standard tones during a low-load and high-load working memory (WM) tasks. Autism-Spectrum Quotient (AQ) and Social Responsiveness Scale (SRS) scores were used as clinical measures in a correlation analysis by using FSL.

Results: Novel stimuli evoked activation in the temporal and prefrontal regions. Activation to novel stimuli was significantly greater during the high-load WM task in the temporal region, but significantly reduced in the frontal regions. AQ and SRS scores were correlated with different brain regions.
Conclusions: Results suggest that the difficulty of a primary task restricts the ability to orient attention to novel sounds and these attention modulation effects are primarily controlled by frontal regions. Examining brain-autistic scores relationship will provide new insights regarding autism.
Supported by a Young Investigator Award from NARSAD

137. Face Processing in the Broad Autism Phenotype: An fMRI Study

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Background: The genetic liability for autism is expressed in non-autistic relatives as characteristics that are milder but qualitatively similar to those seen in autism. This Broad Autism Phenotype (BAP) has also been shown to be associated with social cognition deficits. We investigated the neural substrates of social cognition in the parents of individuals with autism expressing the BAP characteristics using functional magnetic resonance imaging (fMRI). We further examined the association between fMRI activity and the presence of social-emotional processing deficits by classifying the BAP parents as having "aloof personality" (BAP+), or "non-aloof personality" (BAP-), with the goal of identifying a specific endophenotype defining a distinct face-processing style in the BAP group.
Methods: Eighteen BAP-, Twelve BAP+, and seven control parents (parents of neurotypical children) were imaged on a GE 3T MRI scanner (TR: 2000 ms; TE: 27ms; FOV: 256; image matrix: 64 × 64; Flip angle 60; Voxel size: 4 ×4 × 3.8 mm; 34 axial slices). Subjects performed a block-design face- and object-matching task. Image analysis was done with FSL.
Results: The BAP group showed hyperactivation in fusiform gyrus (FG) during both face and object matching compared to control parents. Moreover, BAP+ individuals showed more FG and amygdala activation to faces as compared to the BAP-, who showed an intermediate activation.
Conclusions: BAP individuals showed some similarities to those seen in individuals with autism. These results may provide a window into the endophenotype that may result from a subset of the genes that contribute to social deficits in autism.
Supported by R01MH077843

138. Association of Cortisol Stress Response with Depression and Anxiety Symptoms in Adolescents with Diabetes

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Background: Adolescents with type 1 diabetes have high rates of psychiatric comorbidity which impact long-term medical and psychiatric outcomes. Cortisol, a hormone known to be related to depression and anxiety, acts to increase blood glucose levels during times of stress. The relationships between cortisol responsiveness to stress and (1) diabetes control (2) anxiety symptoms and (3) depressive symptoms were investigated.
Methods: Seventeen adolescents (mean age=15.63yrs) with diabetes were exposed to the Trier Social Stress Test for Children. Salivary cortisol was sampled at baseline and at six 10-minute intervals following the stress procedure. Participants completed interviewer-administered and self-report measures of depression and anxiety. Glycosylated hemoglobin (HbA1C) was assessed to determine diabetes control.
Results: Subjects with poor diabetes control demonstrated lower cortisol response to stress compared to subjects with good diabetes control ($p<.05$). Among female participants, increased anxiety was associated with lower HbA1C, reflecting better diabetes control, and lower cortisol response to stress ($p<.05$). Increased years of diabetes was associated with a low flattened cortisol profile for females only ($p<.05$). Increased depressive symptoms were associated with lower cortisol response to stress for males only.
Conclusions: This study suggests that a relationship between diabetes control, anxiety, and cortisol reactivity exists. Moderate anxiety symptoms may be protective in maintaining good diabetes control for female adolescents. Diabetes diagnosis at a young age may predispose girls to increased anxiety and cortisol dysregulation in response to stressors. Longitudinal investigation in a larger sample is needed to confirm these findings and evaluate the temporal association of these relationships.
Supported by Endowment Fund, The Hospital for Sick Children

139. Grey Matter Volume Correlates with Performance in a Virtual Water Maze Task: A Study of Boys with Androgen Excess

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Background: Sex steroids are implicated in gender-dominant psychiatric disorders. Major questions remain how perturbations of sex steroids such as testosterone impact human development and cognitive function. One cognitive ability associated with testosterone is spatial navigation.
Methods: We tested 10 boys (mean age 11.65 ± SD 2.6) with a rare disorder of androgen excess (Familial Male Precocious Puberty) and 14 healthy boys (mean age 13.99 ± SD 2.4) on a virtual version of the Morris Water Maze task, in which a hidden platform had to be located within a room. In addition, anatomical magnetic resonance images (MRIs) were collected after task completion and performance was correlated with grey matter volume (GMV) in both groups.
Results: Both groups did not differ from one another significantly on behavioural measures although effect sizes were moderate. A double dissociation with regards to brain correlations were apparent in parahippocampus and cerebellum. While patients showed significant associations of GMV with latency to reach the platform in bilateral parahippocampus as well as thalamus and medial frontal cortex, controls exhibited significant correlations with latency and GMV in lateral cerebellum and striatum.
Conclusions: The data indicate an impact of testosterone on brain development in a rare genetic disorder of early excess androgen and suggest that early steroid perturbations may influence cognitive recruitment of underlying neurocircuitry in spatial navigation.
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140. Increased Cortical Excitability after High Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) in Adolescents with Treatment-Resistant Major Depressive Disorder (MDD)

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Background: The motor threshold (MT) is a single-pulse transcranial magnetic stimulation (TMS) measure of cortical excitability. Numerous studies have examined the impact of TMS on cortical excitability and inhibition in adults. Little is known regarding its impact on children and adolescents. This study hypothesized that 30 sessions of 10 Hz rTMS (3000 stimulations per session) applied to the dorsolateral prefrontal cortex would increase motor cortical excitability (decreased MT) as assessed by weekly motor threshold (MT) measurements.
Methods: Seven adolescents with treatment-resistant MDD enrolled in an open trial of 10 Hz rTMS. Resting MTs were obtained by the visualization of movement method with a maximum likelihood threshold hunting computer algorithm at baseline and after each week of treatment (five sessions per week).
Results: A within-subjects mixed model repeated measures analysis was used to examine MT over time (baseline, weeks 2,4,5). The omnibus effect from the mixed model did not reach statistical significance (p=.32), but found a decreasing least squares mean effect in MT from baseline to week 5. Multiple comparisons of each subsequent week to baseline demonstrated a least squares mean decrease in MT, but each comparison was not statistically significant. The mean decrease from baseline to week 5 (-4.46), however, approached a trend level (p=.07).
Conclusions: These pilot results suggest that high frequency rTMS may increase cortical excitability in some adolescents with treatment-resistant MDD. Further work with measures of cortical excitability and inhibition could aid in classification of illness severity or prediction of response to treatment.
Supported by Stanley Medical Research Institute and AACAP Pilot Research Award Supported by Lilly USA LLC

141. Acute Nicotine Effects on Response Inhibition: An fMRI Study of the Stop Signal Task

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Background: Impulsivity is recognized as an important cognitive and behavioral process that is associated with psychopathology such as ADHD and substance abuse including nicotine addiction. We have previously demonstrated that acute nicotine administration improves impulsive responding (behavioral inhibition) in non-smoking adolescents and young adults with ADHD. This study examined the functional neuroanatomy associated with improved behavioral inhibition using the Stop Signal Task during acute nicotine administration in highly impulsive young women.
Methods: 6 non-smoking young adult females who were determined to be highly impulsive as measured by the Stop Signal Task at baseline participated in this study. Subjects received acute nicotine (7 mg patch for 45 minutes) or placebo on separate days. The Stop Signal Task was administered during fMRI scanning to assess changes in behavioral performance and functional neuroanatomy during nicotine administration. The primary dependent variable is the Stop Signal Reaction Time (SSRT) which is an estimate of the speed of inhibiting a response.
Results: Acute nicotine improved behavioral performance seen as faster Stop Signal Reaction Time (SSRT) on this task. Compared to placebo administration, nicotine was associated with a more focal pattern of brain activation in task relevant areas including right inferior frontal gyrus, anterior cingulated cortex and the pre-supplementary motor area.
Conclusions: These findings suggest that in highly impulsive individuals nicotine may improve impulsivity by increasing the efficiency of frontal neural systems. Continued research in this area may help understand the vulnerability to cigarette smoking for individual with ADHD,
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142. Face Processing in Depersonalization Disorder: An fMRI Study of Emotion and Familiarity

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Background: Depersonalization disorder (DPD) is a dissociative disorder characterized by two core phenomenological components: hypoemotionality and unfamiliarity (Simeon et al., 2003). Previous research demonstrated decreases in subcortical limbic activity to increasingly intense happy and sad facial expressions in DPD, (Lemche et al., 2007) suggesting that decreased limbic activation may be a neural correlate of the inexperience of emotion in DPD. Abnormal increases in activation of the dorsal prefrontal cortical regions to emotional stimuli have also been implicated in the hypoemotionality component of DPD (Lemche et al., 2008, Phillips et al., 2001). Familiarity-related stimuli have not previously been studied in the neuroimaging of DPD, although a PET imaging study has implicated a role for altered activation of unimodal and multimodal sensory association areas in perceptual disturbances of DPD under baseline conditions (Simeon et al., 2000).
Methods: 10 adult DPD patients were compared to 10 matched healthy controls. Participants underwent fMRI while viewing faces expressing a variety of emotions including sad, happy, fearful and neutral. Participants also viewed familiar (self, famous) and unfamiliar (stranger) faces.
Results: Preliminary analyses indicate that DPD patients may have dampened limbic responses to emotional faces compared to controls. Preliminary results of the familiarity data suggest patients with DPD may exhibit dampened prefrontal response to familiar faces.
Conclusions: There are no known efficacious pharmacological treatments for DPD (Simeon et al., 2003). Localization of brain regions subsuming the hypoemotionality and unfamiliarity characteristic of the disorder may contribute to the development of targeted somatic treatments, such as transcranial magnetic stimulation.
Supported by MO1-RR00071;from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH)

143. Emotion Regulation of Affective Stimuli in Depersonalization Disorder: Psychophysiological and Subjective Findings

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Background: Patients with depersonalization disorder (DPD) experience a pervasive inability "to feel" (Simeon et al., 2003). This hypoemotionality spans across a variety of emotions and has been linked to prefrontal hyperactivation coupled with limbic hypoactivation in neuroimaging studies (Lemche et al.,

2008; Phillips et al., 2001). However, the capacity of DPD patients to regulate their emotion by actively suppressing or enhancing intensity has not been previously studied, and could have therapeutic implications.
Methods: 14 adults with DSM-IV DPD and 14 healthy controls of similar age and gender performed an emotion regulation task (ERT; Jackson, 2000). Heart rate and skin conductance responses were measured while participants viewed IAPS pictures of positive, neutral, or negative valence and were asked to maintain, suppress, or enhance their emotional response to each picture (neutral pictures were always followed only by the maintain instruction). Participants then subjectively rated their emotional valence, from negative to positive, elicited on a 9-point Likert-type scale.
Results: No group differences were found for heart rate or skin conductance. However, the two groups differed significantly on subjective emotional intensity ratings as a function of emotion regulation instruction and stimulus valence (ANOVAR: group x instruction, $p < .05$, two-tailed; group x instruction x valence, $p < .05$, two-tailed).
Conclusions: It appears that active emotion regulation can subjectively impact the emotional experience of patients with DPD, although the psychophysiological measures were not sensitive to these phenomena; event related potentials (ERP) could be used to investigate the neurophysiological underpinnings of emotion regulation disturbances in DPD.

144. Preliminary Evidence for Cannabinoid Receptor CB1 Polymorphisms in Cannabis-Induced Chronic Depersonalization

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Background: Approximately 13% of all individuals with DSM-IV-TR Depersonalization Disorder (DPD) report onset acutely triggered by cannabis ingestion.[1] Often, very sporadic lifetime use of cannabis can precipitate a chronic and refractory depersonalization syndrome.[2] Despite this striking phenomenon, genetic vulnerability factors for DPD including the cannabinoid receptor genes have not been investigated.
Methods: In an attempt to identify polymorphisms which may be associated with cannabis-induced depersonalization, all exons of the CB1/Cnr1 gene were sequenced in 14 Caucasian adults with DPD who reported an undisputed acute temporal association between marijuana use and onset of chronic depersonalization.
Results: Most patients (9/14) reported cannabis lifetime use <10x prior to depersonalization onset (*mode*=2; *median*=4); all abstained after onset. Genetic sequencing revealed a novel 2 base pair insertion deletion polymorphism located in non-coding exon 3 roughly 330 bases distal (3') to the rs2023239 SNP in 3 individuals (p=.055). We also found 5 novel SNPs, although none were in protein coding sequences. Finally, all participants had at least one 'G' allele for the rs1049353 SNP.
Conclusions: The findings of this small sample may implicate CB1 gene variations in chronic depersonalization. DPD patients are generally non-responsive to psychopharmacological treatments; similarly the 'G' allele of the rs1049353 SNP has been associated with medication resistance in psychiatric disorders such as schizophrenia[3] and depression.[4] Association of the CB1 gene with alcohol and drug use disorders[5-7] is also consistent with our findings. These promising preliminary data warrant further investigation in large samples of cannabis vs. non-cannabis triggered DPD and appropriate control groups.
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145. Temporo-Parietal Junction Stimulation in the Treatment of Depersonalization Disorder

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Background: Depersonalization Disorder (DPD) is a condition for which no efficacious treatments exist. We present results of the first trial testing repetitive Transcranial Magnetic Stimulation (rTMS) effects on temporo-parietal junction (TPJ), previously found to be hyperactive in DPD.
Methods: Twelve DPD patients (M/F=9/3; Mean Age=33.6 years, S.D.=12.9) were treated with inhibitory (1-Hz) rTMS to the TPJ for 6 weeks. Response to treatment was defined as a ≥ 50% decrease on the Cambridge Depersonalization Scale (CDS). Patients who showed at least 25% decrease on the CDS after 3 weeks of right TPJ stimulation received 3 more weeks of right TPJ rTMS to test whether additional rTMS might be beneficial. The others were crossed over to 3 weeks of left TPJ rTMS to test for a lateralized effect of rTMS on DPD.
Results: After 3 weeks of right TPJ rTMS the entire sample showed 24% reduction in the CDS, from 114±41 to 87±47 (p=0.002). In those patients (n=5) who received 6 weeks of right TPJ rTMS, DPD symptoms showed 68% improvement, with a significant CDS total score decrease from 113±52 to 36±30 (p=0.002). Four patients withdrew after the first 3 weeks; those who crossed over to left TPJ rTMS (n=3) showed 7% improvement after 6 weeks. No side effects were noted in any patients.
Conclusions: Low-frequency rTMS to the right TPJ resulted in significant clinical improvement in 5 out of 12 patients. A larger sample and a sham-controlled design will be needed to test the relevance of these promising although preliminary findings.

146. Contrasts in Taste Reward Expectation vs. Unexpected Receipt in Bulimia Nervosa

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Background: Eating disorders are marked by perturbations in interpretation of food as reward. The temporal difference model tests brain response to unexpected receipt or omission of reward stimuli, which creates a "prediction error signal" (PE) with surge or suppression of brain dopamine. This brain reward prediction response has not been previously studied in bulimia nervosa (BN).
Methods: 17 BN (mean age 25y±6) and 19 control women (mean age 24y±5) underwent functional magnetic resonance imaging (fMRI) while receiving 1mL samples of randomized unconditioned taste stimuli (US) of 1 molar sucrose (n=100), artificial saliva (n=80) or no-solution (n=100); each taste condition was associated with its own abstract visual image as conditioned stimulus (CS), preceding US taste delivery. Among these trials, 20% had a "wrong" CS preceding the US sucrose or no-solution, yielding an unexpected receipt or omission of expected US sucrose.
Results: BN receiving unexpected sucrose, compared to controls, showed *decreased* PE in pons and left insula ($p < .01$). BN receiving unexpected nothing showed *decreased* PE in pons, bilateral insula and amygdala ($p < .005$). BN receiving expected sucrose showed *increased* signal in ventral tegmental area ($p = .007$).
Conclusions: BN showed a greater reward response to expected reward, while showing a decreased prediction error response when reward status was unexpectedly changed. These may indicate an increased salience of *expectation* of food reward, and a blunted response to its actual presence or absence. This could help to explain the excessive appetitive food-reward-seeking behavior seen in BN.
Supported by Klarman Family Foundation

147. Taste Challenge with a High Fat Stimulus Reveals Altered Striatal Response in Anorexia And Bulimia Nervosa after Recovery

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Background: We have previously shown that patients recovered from anorexia nervosa (AN) and bulimia nervosa (BN) have altered insula-striatal responses to a sucrose challenge which are hypothesized to mediate hedonic responses to the taste of food (Wagner, Neuropsychopharm. 2008, Oberndorfer, SOBP 2008).
Methods: Brain responses to a high fat cream stimulus were now investigated in individuals recovered from anorexia nervosa (AN, n= 15), bulimia nervosa (BN, n = 12) and compared to a healthy control sample (CW, n=17) using fMRI. Data were analyzed on a Region of Interest based analysis.
Results: Preliminary results of a group analysis (AN,BN,CW) showed a significant difference in the left anterior ventral striatal region (F=7.071, p=0.002) when cream was contrasted with a neutral water solution. A post hoc analysis revealed that women with BN demonstrated elevated neuronal response in contrast to AN (p=0.002) and CW (p=0.032).
Conclusions: Neuronal activation patterns found in response to a high fat challenge correspond to those of a sweet stimulus. These findings suggest disturbed reward regulation in AN and BN which might contribute to under- and overeating, respectively.

148. The Impact of the Anti-Obesity Drug on Brain Responses to Food Images in the Fasted and Fed States

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Background: Sibutramine is centrally-acting anti obesity drug. Little is known about its precise mechanism of action and how administration of this drug results in long term weight loss. Insights gained in this area may aid the design and understanding of future and more efficacious, anti-obesity therapies.
Methods: A randomised, cross over, placebo controlled study of overweight/obese volunteers was performed. The brain activity in response to high and low calorie food images was measured using functional magnetic resonance imaging. In particular we explored the effects of the drug on these responses in both the fasted and fed states.
Results: Significant striatal, hypothalamic and amygdala activations were observed in response to high calorie food images. Striatal responses were greater when the images were viewed by the participant in a fasted rather than fed state. While the drug produced suppressions in hypothalamic and amygdala responses to high calorie food images, its action was not specific to fasting state.
Conclusions: A number of brain regions are responsive to high calorie in preference to low calorie food images. While certain responses are augmented by fasting, the action of Sibutramine appears to persist across both fasted and fed states.
Supported by Glaxo Smith Kilne

149. Differentiating the Attention Abnormalities Undermining Affect Regulation in Psychopathy and Externalizing Disorders

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Background: Psychopathy and Externalizing are both disinhibitory syndromes attributed to dysfunctional cognitive/affective interactions. Yet, the etiological underpinnings of these syndromes are essentially opposite. Psychopathy is associated with an early attentional bias that undermines sensitivity to affective information and the initiation of self-regulation once attention is engaged in goal-directed behavior (Newman et al., in press). Conversely, externalizing involves difficulty using late selective attention to overcome events of motivational significance (Patrick et al., in press). Consequently, they are hypersensitive to salient cues and less able to regulate emotion responses. This study examines the effects of early and late attentional focus on threat processing in these two groups.
Methods: We evaluated fear-potentiated startle (FPS) in 97 offenders under four experimental conditions that crossed attentional focus with early versus late onset of the threat-relevant cues. Psychopathy and externalizing were assessed using Hare's Psychopathy Checklist-Revised and subscales from the Multidimensional Personality Questionnaire-Brief.
Results: Psychopaths displayed a significant deficit in FPS in the early alternative-focus condition in which threat cues appeared after the goal-directed focus was established (early attention bias). Demonstrating a deficit in late selective attention, externalizers displayed significantly greater FPS in the strong threat-focus condition, when threat cues occurred first, and weaker FPS when threat-irrelevant cues preceded the threat-relevant information, implicating hypersensitivity to whichever stimulus was presented first.
Conclusions: These results support the hypothesis that Psychopathy and Externalizing are differentially associated with early- and late- selective attention abnormalities. This differential association provides a meaningful target for clinical intervention.
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150. Exaggerated Amphetamine-Induced Dopamine Release in Striatal and Extrastriatal Regions Predicts Attentional Dyscontrol in Healthy Individuals

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Background: Attentional dyscontrol is a common feature among externalizing disorders, such as attention deficit hyperactivity disorder (ADHD), antisocial personality disorder (APD), and substance abuse. Dopamine (DA) is well known to critically regulate attention, and dopamineric dysfunction has been proposed to be a shared pathophysiological mechanism within the externalizing spectrum. While preclinical work has demonstrated regionally selective effects of manipulating dopamine on attentional performance, the specific neurobiological substrates for interindividual differences in attentional control are still poorly characterized, particularly in humans. To investigate the relationship between

mesocorticolimbic DA function and human attentional performance, we employed DA receptor imaging using the D2/D3 selective ligand [18F]fallypride in concert with the DA agonist d-amphetamine (AMPH).
Methods: Thirty-four physically and psychiatrically healthy volunteers completed the Tests of Variables of Attention (TOVA), a visual continuous performance test, prior to participating in a two day, single-blind, placebo-controlled protocol. For each subject, we calculated a composite measure of attentional control, and a measure of response sensitivity (D'). A random-effects general linear model SPM analysis was used to assess the relationship between attentional performance and DA neurochemistry.
Results: Diminished attentional control predicted exaggerated AMPH-induced DA release in aspects of the ventral striatum and basal forebrain. Poorer response sensitivity (D') was also associated with enhanced ventral striatal DA release, and additionally predicted exaggerated DAergic responses to AMPH in the anterior cingulate and ventrolateral prefrontal cortex.
Conclusions: These findings suggest that hypersensitivity to stimulation within the mesocorticolimbic DA system may be an important element of attentional dyscontrol, and further link dopaminergic dysfunction to risk for externalizing disorders.
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151. A Common, Population-Specific Stop Codon in HTR2B Co-Segregates with Severe Impulsivity

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Background: Impulsivity, describing action without foresight, is an important feature of several psychiatric diseases and suicidal behavior. The aim of this study was to find uncommon variants and to test for association with impulsive behavior.
Methods: Fourteen genes involved in serotonin and dopamine neurotransmission were resequenced, via Solexa, in 96 unrelated Finnish males violent offenders with DSM-III-R diagnosis of Antisocial Personality disorder, Borderline Personality disorder and Intermittent Explosive disorder, and 96 healthy controls. Cases had elevated Brown-Goodwin Lifetime Aggression scores (23.7, SD ± 4.9) compared to controls (8.1, SD ± 4.9).
All non-synonymous SNPs identified were genotyped in a larger Finnish sample and in 89 pedigrees.
Results: A stop codon, Q20*, was detected in the HTR2B gene. Q20* blocks the expression of the 5-HT2B receptor, it is common (frequency of 0.01 in controls) and apparently exclusive to Finns. Q20* was associated with impulsivity in the case/control dataset ($p = 0.007$) and co-segregated with impulsive behavior in families ($p = 0.013$).
The 17 Q20* heterozygous cases identified, with no evident cognitive impairment, were convicted for unpremeditated violent crimes committed under influence of alcohol. No antisocial behavior was present when not alcohol intoxicated. CSF testosterone was significantly higher in Q20* violent offenders than in controls.
Conclusions: This study shows the potential for identifying and tracing effects of rare alleles in complex behavioral phenotypes using deep sequencing in founder populations and families, and suggests a role for HTR2B in impulsivity.

152. Evidence of Association between the Leptin Receptor (lepr) Single Nucleotide Polymorphism (snp) Rs3806318 and Suicide Attempts In Females

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Background: The evidence linking low serum cholesterol and leptin to suicidal behaviors, particularly if violent, is mounting. The leptin receptor single nucleotide polymorphism (SNP) rs3806318 has been associated with substance abuse and major depression. The main aim of this study was to explore the relationship between one SNP (rs3806318) of the leptin receptor (LEPR) gene and suicidal behavior.
Methods: Sample: 1079 subjects [suicide attempters (n=389), psychiatric inpatients (n=333), and healthy controls (n=357)]. Genotyping: Genomic DNA was extracted from peripheral blood samples. Based on central nervous system (CNS) transmitter systems, we selected 1174 SNPs from 312 candidate genes involved in several physiological pathways using public databases (dbSNP, HGVbase, TSC, HapMap). They were genotyped using the SNPlexTM platform according to manufacturer instructions. Genotype and allelic distribution at each of the SNP loci were previously determined by direct counting in all samples. All SNPs were tested for Hardy-Weinberg-equilibrium. Statistical analyses: we used chi square analyses to test if an association between the LEPR rs3806318 and suicide attempter status exists.
Results: we found a statistically significant association between LEPR rs3806318 SNP and suicide attempter status in females ($X2=1.201$, $df=4$, $p=0.017$).
Conclusions: The results showed an association between LEPR rs3806318 and suicide attempts in females. The rs3806318 SNP has previously been associated with substance abuse and depression. However, there are no previous reports on the relationship between rs3806318 and suicidal behavior so far. Our results suggest that some biological factors underlying suicidal behavior might be different in men and women.
Supported by CIBERSAM

153. Increased Brainstem 5-HT Reuptake Transporters (SERT) in Males with Extreme Levels of Impulsive Aggression: A PET Study Using 11C-DASB.

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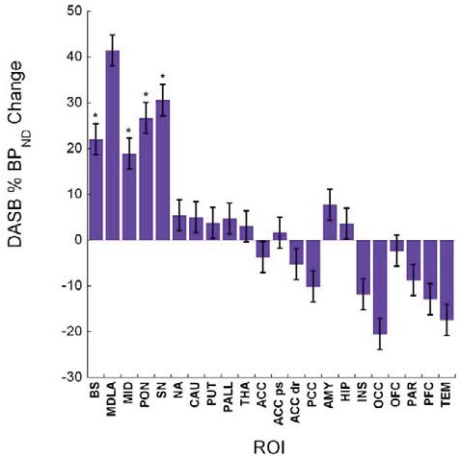
Background: Reduced availability of 5-HT reuptake transporters (SERT) in the anterior cingulate (ACC) of personality disordered patients with impulsive aggression (IA) has been reported using positron emission tomography (PET) (Frankle, 2005). We aimed to independently replicate and extend this finding in a population-derived sample while controlling for potentially confounding callous-unemotional (CU) personality traits.
Methods: Healthy male volunteers were recruited with IA ratings in the high and low population extremes (more than 1.5 SD below or above the mean).

High-IA (n=10) and low-IA (n=12) groups were well matched for age (33±9 yr), IQ (93.1±7.6), BMI (26.4±3.0) and low CU ratings. Regional SERT binding potentials (BPND) were derived from 11C-DASB PET data (HRRT camera) using Logan graphical analysis with arterial input function, and compared between groups. Correlations were measured between SERT BPND and IA measures, neuropsychological performance, and childhood adversity.

Results: In the high-IA group, SERT were significantly increased in brainstem regions (+29.4±9.3%; p<0.001), modestly reduced across neocortical regions (-2.3±6.5%; p=0.03), and unchanged in ACC, striatum, thalamus, hippocampus and amygdala. Across individuals, brainstem SERT BPND was significantly (p<0.05) positively correlated with IA measures, set-shifting errors, deficient response inhibition, risk-taking, childhood trauma and stressful early life events.

Conclusions: Our data support the conclusion that serotonergic function is dysregulated in males with high IA, with SERT substantially increased in brainstem and modestly reduced across neocortex. We did not replicate previous findings of reduced SERT in ACC. The correlation with childhood adversity scores suggests that the dysregulation may be (at least partially) neurodevelopmental in origin.



154. Relationship between DTI White Matter Abnormalities and Impulsivity in OIF/OEF Combat Veterans with Blast-Related Mild TBI

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Background: The problem of blast-related traumatic brain injury, particularly mild TBI (mTBI), is not well understood. To our knowledge, no work has been done using in vivo measures to examine the relationship between brain function, aggression, and impulsivity in returning combat veterans from Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) with diagnoses of blast-related mTBI. Fractional anisotropy (FA) using diffusion tensor imaging (DTI) provides a measure of the integrity of white matter fibers in the brain and is an important technique in TBI studies.

Methods: Diffusion-tensor images were obtained on eight combat veterans (mean age=29.4±6.4 years) with blast-related mTBI and ten healthy controls (mean age=28.9±6.4 years). Blast mTBI was diagnosed as per established guidelines and clinical-case consensus between treating clinicians. White matter FA was computed in cortical Brodmann areas (BA) using a semi-automated technique. Impulsivity was assessed by the Barratt Impulsiveness Scale and anger and aggression was assessed with the State-Trait Anger Expression Inventory-2 and the Buss-Perry Aggressiveness Questionnaire. Based on prior work, we hypothesized the mTBI group would show higher levels of FA in the prefrontal cortex, and these abnormalities are associated with higher impulsivity and aggression.

Results: Compared with controls, blast-related mTBI subjects demonstrated higher FA values in anterior frontal, orbitofrontal, and dorsolateral prefrontal cortex (GroupxPrefrontal region interaction, F(6,114)=2.34, p=0.04). Among the mTBI group, higher FA in DLPC (BA44) and parts of OFC (BA45) was associated with greater impulsivity and aggression.

Conclusions: Findings suggest a complex relationship between white matter abnormalities and self-reported ratings of impulsivity/aggression.

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155. Genetic Vulnerability to Inflammation-Related Major Depressive Disorder is Influenced by Age

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Background: Genetic predispositions for MDD may differ depending on the nature of the MDD precipitant, complicating the search for genetic vulnerability. Exogenously administered interferon-α is one potent and robust precipitant of MDD, although most patients are resilient to this side effect, making this a good model for examining genetic vulnerability. However, even in this relatively homogenous situation, the contribution of various genes may be influenced by age.

Methods: Of 209 patients with hepatitis C, 117 began treatment with interferon-α (IFN-α), an exogenous cytokine. We prospectively determined the incidence of MDD during treatment and psychiatric symptoms using the BDI-II, PSQI, and AIAQ. We examined candidate polymorphisms in the serotonergic, growth factor, and inflammatory systems. Subjects were grouped into younger (age <50) and older patients and examined for MDD incidence (survival analyses) and worsening symptoms (repeated-measure mixed-effect analyses).

Results: 26.5% developed MDD. Genetic variability in the serotonin transporter, tryptophan hydroxylase, and brain-derived neurotrophic factor - along with sleep quality and IL-6 -- all influenced the likelihood of developing MDD. BDNF polymorphisms and peripheral IL-6 levels were specifically influential in older subjects (X^2 = 6.3; p<0.05: X^2 = 4.3 p<0.05 respectively), while the serotonin transporter and TNF-α polymorphisms were specifically influential on mood symptoms in younger adults. Poor sleep quality was influential (Hazard Ratio = 4.5; p<0.001) regardless of age.

Conclusions: These findings support the interaction of various systems (inflammation, serotonin, and growth factors) in the pathophysiology of MDD. Moreover, the affect of each on inflammation-related MDD vulnerability is influenced by age.

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156. Regional Urocortin 1 Response to Chronic Social Defeat and Desipramine Treatment

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Background: The urocortins are three distinct neuropeptides that are recognized by the type 1 and type 2 CRF receptors. We examined the response of urocortin 1 protein in brain regions of rats subjected to a regimen of chronic social defeat with or without desipramine (10 mg/kg).

Methods: Adult, male, Sprague-Dawley rats (225 g) were individually housed with access to water restricted to two hours per day with a choice of plain tap water or a 2% sucrose solution. Defeat was applied once per 9-10 days for nine weeks before beginning desipramine treatment in half of the defeated rats and half of the controls with vehicle administration to the non-desipramine treated groups. Four weeks after desipramine treatment was begun, sucrose consumption deficits in the defeated rats was normalized by desipramine and rats were euthanized by guillotine without anesthesia. Brain regions were dissected and urocortin 1 protein was measured by RIA.
Results: Sucrose consumption in the vehicle/defeat group was significantly decreased relative to the other three groups. Corticosterone was not significantly different one day after the last defeat. Urocortin 1 was significantly decreased by chronic social defeat in the cerebellum and entorhinal cortex and was significantly increased in the dorsal brain stem and locus coeruleus. Desipramine treatment significantly increased urocortin 1 in the dorsal raphe and locus coeruleus and decreased urocortin 1 in the enthorhinal cortex.
Conclusions: These results indicate that urocortin 1 responses are found in different regions and groups after chronic social defeat and desipramine treatment compared to CRF.
Supported by American Foundation for Suicide Prevention Grant

157. 5-HTTLPR Genotype, Chronic Fluoxetine Administration, and Cortical TREK1 Protein Expression in Rhesus Monkeys

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Background: TREK1 and TRAAK are background potassium channels that are widely expressed throughout the brain and contribute to the overall excitability of neurons. TREK1 knockout mice show a depressive resistant phenotype and fluoxetine inhibits TREK1. TRAAK has not been shown to be regulated by neurotransmitters. This study examined if 5-HTTLPR genotype and chronic fluoxetine treatment affect TREK1 and TRAAK protein expression in prefrontal cortex of male rhesus monkeys. We hypothesized that genetically or pharmacologically reduced serotonin transporter efficiency would be associated with reduced TREK1, but not TRAAK, protein expression. This study is continuing with female rhesus monkeys currently undergoing treatment.
Methods: Twelve male Rhesus monkeys were treated with fluoxetine (5-HTT genotypes n: s/s=1, s/l=1, l/l=4) or a vehicle-alone (5-HTT genotypes n: s/l=2, l/l=4) for 39 weeks. TREK1 and TRAAK levels in Brodmann area 10 were assessed by Western blotting.
Results: Neither TREK1 nor TRAAK differed across treatment groups (ps>.29). For TREK1, a trend emerged for 5-HTTLPR genotype (p=.09), driven by reduced TREK1 protein expression in short allele carriers compared to long homozygotes. TRAAK was not significantly affected by 5-HTTLPR genotype.
Conclusions: Chronic antidepressant treatment did not affect cortical TREK1 protein expression. However, preliminary evidence suggests that 5-HTTLPR genotype may affect TREK1 levels. Theoretical work postulates that SSRIs may directly and/or indirectly (via 5-HT1A desensitization) inhibit TREK1. This preliminary work offers support for the hypothesis that TREK1 inhibition results from elevated 5-HT levels leading to 5-HT1A desensitization but does not preclude the possibility that SSRIs may directly inhibit TREK1. RR17701.
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158. 17b Estradiol Decreases the Stress Induced Acquisition of Learned Helplessness in Female Rats

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Background: Low levels of estrogen are correlated with increased stress reactivity and the development of premenstrual dysphoric disorder, postpartum and major depressive disorder in women. Several studies have described the antidepressant effects of 17β estradiol (E2) in rodents, but it is unknown how ovarian hormones modulate stressful experiences and influence the development of maladaptive behaviors, such as poor escape learning and helplessness.
Methods: We investigated the effect of E2 on the acquisition of depression-like behavior in ovariectomized (OVX) rats using the Learned Helplessness (LH) model of depression. Induction of LH involves exposing rats to inescapable shock (0.65 mA) followed by escape testing. Animals that do not learn to escape are considered to be helpless.
Results: OVX rats were treated with either E2 (10 μg/kg; proestrous levels:80-120 pg/ml) or vehicle (VH;oil) prior to escape testing. Importantly, E2 animals demonstrated significantly shorter escape latencies than VH treated rats. To test whether E2 could reverse LH, OVX rats that reached criteria for LH were treated with E2 or VH for 2 days prior to retesting. While all VH animals remained helpless during retesting, 40% of E2 treated rats learned to escape and no longer demonstrated LH.
Conclusions: Our results show that high levels of E2, such as those found in proestrus, can protect against the acquisition of LH and reverse previously established depression-like behavior, indicating that E2 modulates stress reactivity and limits the development of LH. Further studies will determine the mechanism by which E2 protects neuronal circuits affected by aversive stimuli.
Supported by NARSAD

159. Possible Involvement of Bax Inhibitor 1 (BI-1), A Modulator for Endoplasmic Reticulum (ER) Cellular Stress, in Affective Resilience

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Background: The purpose of this study was to examine the role of a modulator of ER stress in behavioral models of affective resilience. ER stress is a cellular stress response due to the accumulation of unfolded or misfolded protein in the lumen of the ER. This process has been implicated in numerous diseases such as bipolar disorder and depression. Moreover, mood stabilizing drugs and antidepressants increase ER stress proteins. We examined whether ER associated protein, BI-1, whose primary function is to modulate ER stress pathways may have protection against behavioral stress and anhedonia.
Methods: We developed two different measures of hedonic activity in mice, as well as, using the well validated learned helplessness model to determine whether BI-1 overexpression (OE) produces protection against behavioral stress and anhedonia.
Results: Our results show that BI-1 OE mice were protected against anhedonia following two different depletion models (serotonin and catecholamine depletion) compared with wild type (WT) controls. We also observed lower rates of spontaneous recovery following induction of learned helplessness by measuring escape latencies in active avoidance in WT compared to BI-1 OE mice. In order to explore the potential mechanism of BI-1 OE, we utilized an

ER stress-inducing chemical, Thapsigargin (Tg). In primary cortical mouse cultures, we found that BI-1 OE cultures decreased basal cytosolic calcium levels and decreased calcium cytosolic accumulation following challenge with Tg as compared to WT neuronal cultures.
Conclusions: These findings taken together warrant further study into BI-1 as a protective factor in stress and anhedonia.
Supported by NIMH IRP

160. Activation of ERK1/2 and Akt Signal Pathways in the Brain of Ouabain Rat Model for Mania

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Background: Intracerebroventricular (ICV) injection of ouabain, a specific Na-K ATPase inhibitor, induced behavioral changes in rats, a putative animal model for mania. The binding of ouabain to Na-K ATPase has been known to affect signaling molecules *in vitro* including ERK1/2 and Akt, however, the effects on *in vivo* brain has not been elucidated yet.
Methods: After ICV injection of ouabain in rats, we investigated the changes in ERK1/2 and Akt signal pathways in rat striatum, frontal cortex, and hippocampus along with changes in locomotor activity.
Results: Ouabain acutely induced the biphasic dose-dependent changes in locomotor activity during 30 min. The phosphorylation of ERK1/2 and Akt in rat brain showed dose-dependent changes similar to those observed in locomotor activity with relatively high correlation. Phosphorylation of MEK1/2 and p90RSK, up- and down-stream kinase of ERK1/2, changed with ERK1/2 phosphorylation. In addition, phosphorylation of GSK-3β, FOXO1, and eNOS, substrates of Akt, showed similar changes. Moreover, single treatment of ouabain with 1 mM induced hyperactivity of rats during 8 hrs, which were accompanied with prolonged increase in phosphorylation level of ERK1/2 and Akt signal pathways until 8 hrs.
Conclusions: Ouabain induced acute dose-dependent changes in ERK1/2 and Akt signal pathways along with those in locomotor activity, and activation of locomotor activity and ERK1/2 and Akt signal pathways by higher concentration of ouabain were maintained until 8 hrs after single treatment, which suggest the possible important roles of ERK1/2 and Akt pathways in behavioral changes of ouabain rat model for mania.
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161. Role of the NMDA Receptor NR2B Subunit in Mediating Anxiety- and Depression-Like Behaviors

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Background: NMDA receptors are increasingly implicated in mood and anxiety disorders. For example, recent studies have shown antidepressant efficacy for NR2B subunit-specific NMDAR antagonists in depressed patients[1]. Here, we investigated the role of NR2B in anxiety- and depression-related behaviors by postnatally deleting NR2B in principle neurons of the cortex and CA1 subregion of the hippocampus in mice[2].
Methods: Corticohippocampal NR2B knockout mice ($NR2B^{KO}$)[2] were phenotyped for anxiety-like (dark/light emergence test, stress-induced hyperthermia) and depression-related behavior (sucrose preference, forced swim test, novelty-induced hypophagia). Responses to chronic exposure to stress were tested via repeated forced swim exposure.
Results: There was a consistent trend for $NR2B^{KO}$ mice to show less anxiety- and depressive-like behavior than non-mutant controls, but this was not a robust phenotype. However, $NR2B^{KO}$ mice exhibited significantly less 'depressive-like' immobility than controls with repeated forced swim exposure (genotype x exposure interaction $F_{9,22}$=1.99 p=0.05).
Conclusions: Deletion of NR2B in principle cells of the dorsal CA1 hippocampal subregion and the cortex did not have strong effects on basal anxiety- or depression-related behaviors, consistent with previous evidence that these brain regions do not play a major role in mediating these basal behaviors[3]. Interestingly, however, loss of NR2B in these regions was sufficient to prevent the development of 'depressive-like' behavior in the face of repeated stress, suggesting an important role for the subunit in the neuroplastic changes accompanying stress.
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162. Characterization of the Ankyrin 3 Bipolar Disorder Risk Gene in Mice

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Background: Recent genome-wide association studies have identified ankyrin 3 (ANK3) as a risk factor for bipolar disorder (BP). ANK3 encodes the scaffold protein ankyrin G, whose neural functions include localizing ion channels and GABAergic synapses at the axon initial segment, neuronal polarity, and synaptic function.
Methods: To elucidate the role of ankyrin G in BP, we assessed the behavioral profile induced by Ank3 reduction in mouse brain. Lentiviral-mediated RNA interference was used to knock down Ank3 expression in hippocampus or nucleus accumbens of adult C57BL/6J mice. Mice were assessed for a range of affective behaviors, intermediate phenotypes of BP, and behaviors mediated by the targeted brain regions, as well as phenotype modulation following sub-chronic mood stabilizer treatment. Further, immunohistochemistry was used to examine the impact of chronic mood stabilizer treatment on ankyrin G expression in the brain.
Results: Ank3 knockdown in the hippocampus or nucleus accumbens resulted in similar phenotypes that recapitulated some of the clinical symptoms of BP, and were partially reversed by lithium treatment. Furthermore, chronic mood stabilizer treatment significantly altered ankyrin G expression at the neuronal AIS in the hippocampus.
Conclusions: These results provide insight into the function of ankyrin G in mediating behavior and its modulation by mood stabilizer treatment. Future manipulations of ankyrin G in mice, including creation of genetically accurate knock-in and humanized mouse models carrying the BP risk variant(s), will provide additional in vivo models for testing novel BP therapeutics and for neurobiological studies to delineate ankyrin's role in BP etiology.
Supported by The Stanley Medical Research Institute

163. Omega-3 Fatty Acid Deficiency Increases Plasma Proinflammatory Cytokine Levels in Rats: Normalization with Omega-3 Fatty Acid Supplementation

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Background: Omega-3 (n-3) fatty acid deficiency and elevated proinflammatory cytokine levels have been implicated in the pathophysiology of mood disorders. To evaluate a causal relationship, we determined the effects

of n-3 fatty acid deficiency on plasma levels of proinflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor alpha (TNF), and C-reactive protein (CRP), and determined reversibility following chronic dietary n-3 fatty acid supplementation.
Methods: Male rats were maintained on a diet with or without the dietary n-3 fatty acid precursor, alpha-linolenic acid (ALA, 18:3n-3), throughout perinatal development (E0-P90). A subgroup of ALA-deficient rats received chronic (30 d) dietary ALA supplementation from P60-P90. At P90, erythrocyte fatty acid composition was determined by gas chromatography, and plasma cytokine levels determined with a multiplexing suspension array Luminex system.
Results: Consistent with prior studies, perinatal ALA deficiency decreased erythrocyte n-3 fatty acid composition, and increased indices of n-6 fatty acid biosynthesis (20:3/18:2 and 20:4/18:2 ratios) and erythrocyte arachidonic acid (20:4*n*-6) composition. N-3 fatty acid deficiency was associated with significant elevations in plasma IL-6 (+63%, p=0.009), TNF (+59, p=0.005), and CRP (+75%, p=0.001) relative to controls. Chronic dietary ALA supplementation normalized erythrocyte n-3 and n-6 fatty acid composition, and significantly reduced plasma IL-6, CRP, and TNF levels relative to n-3 deficient rats.
Conclusions: These preclinical data demonstrate that n-3 fatty acid deficiency, and associated elevations in n-6 fatty acid biosynthesis, robustly increase proinflammatory cytokine levels. Furthermore, elevations in n-6 fatty acid biosynthesis and elevated cytokine levels are reversible with chronic dietary n-3 fatty acid supplementation.
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164. Perinatal Omega-3 Fatty Acid Deficiency Alters Regional Brain Activity in Adult Rats: An in Vivo Magnetic Resonance Imaging Study

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Background: Mood disorders are associated with omega-3 (n-3) fatty acid deficits and abnormalities in cortical activity measured by magnetic resonance imaging (MRI). However, the relationship between cortical deficits in docosahexaenoic acid (DHA, 22:6*n*-3), the principle n-3 fatty acid in gray matter, and regional brain activity is not known.
Methods: Perinatal (E0-P90) and post-weaning (P21-P90) alpha-linolenic acid (ALA, 18:3*n*-3) depletion models were used to generate graded cortical DHA deficits. In adulthood (P90), ALA+ controls (n=8) and perinatal (n=8) and post-weaning (n=8) ALA- rats were anesthetized with 1.5% isoflurane, and positioned in a 7T Bruker Biospec system with a 38 mm Doty Litz coil. Blood oxygen level-dependent (BOLD) activity data were analyzed with SPM5, and group differences were considered significant at p<0.05(corrected). Postmortem cortical DHA composition was determined by gas chromatography.
Results: Relative to controls, cortical DHA composition was significantly reduced in adult post-weaning (-28%, p<0.0001) and perinatal (-68%, p<0.0001) ALA- groups. Relative to controls, post-weaning ALA- rats exhibited decreased BOLD activity in the superficial layers of the cortex, lateral septum, dorsal hippocampus, and hypothalamus, and greater BOLD activity in the orbitofrontal cortex, medial layers of frontal cortex, dorsal striatum, ventral hippocampus, entorhinal cortex, and cerebellar cortex. Relative to controls, perinatal ALA- rats exhibited lower left lateralized BOLD activity largely restricted to cortical mantle and dorsal striatum, and greater right lateralized BOLD activity in the cerebral and cerebellar cortices.
Conclusions: These data demonstrate that brain DHA deficits are associated with significant abnormalities in regional brain activity in the adult rat.
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165. Effects of Housing Conditions in the Reduction of Submissive Behavior Model of Antidepressant Activity

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Background: To improve the translation of preclinical findings to clinical outcomes for depressed patients, better preclinical models are needed. The Reduction in Submissive Behavior Model (RSBM) was recently developed to predict antidepressant activity (Malatynska & Knapp, *Neurosci Biobeh Rev*, 2005). In this model, a subset of randomly-paired rats forms dominant-submissive relationships (DSR) when subjected to competition for a food reward in a specially designed apparatus. If the submissive animal of the pair is treated with antidepressant drugs (and the dominant animal is treated with vehicle) over a three week period, the DSR is altered and the submissive and dominant animal eventually spend equal time consuming the food. In an effort to improve the utility of this model, we examined the effects of housing conditions on the stability of the DSR.
Methods: Randomly paired male, Sprague-Dawley rats were housed in separate groups (four animals per cage) or together (two animals per cage) over the course of the five-week period of the RSBM. Time spent on the feeder was measured by computer software (TopScan, Cleversys Inc.).
Results: No significant difference in the number of pairs formed, or the stability of the DSR over time, was observed between the two groups. Administration of the MAOI phenelzine produced a significant decrease in dominance level for paired-housed animals.
Conclusions: Housing paired-animals together or separately did not alter the stability of the DSR in the RSBM. The effects of phenelzine and other antidepressants in the assay will be discussed.
Supported by Eli Lilly & Co.

166. Increasing Adult Hippocampal Neurogenesis is Sufficient to Enhance Cognition but not Mood

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Background: Understanding how neural circuit-plasticity mechanisms may be harnessed to improve cognition and mood is essential for developing novel treatments for psychiatric disorders. Adult hippocampal neurogenesis is a unique form of plasticity that generates new neurons in the dentate gyrus throughout life. Levels of adult hippocampal neurogenesis are elevated by interventions associated with beneficial effects on cognition and mood such as exercise and chronic antidepressant treatment. These properties of adult hippocampal neurogenesis suggest that it may be harnessed to improve hippocampal functions. However, it is not known whether stimulation of adult hippocampal neurogenesis is sufficient to improve cognition and mood.
Methods: We employ a novel genetic gain-of-function strategy in which adult hippocampal neurogenesis can be inducibly augmented in a cell-autonomous manner.
Results: Mice in which the pro-apoptotic gene Bax is ablated selectively in adult neural stem cells show a two-fold expansion in the population of excitable adult-born neurons and a significant enhancement in neurogenesis-dependent LTP. Mice with increased adult hippocampal neurogenesis show normal object recognition, rapid one trial contextual encoding, extinction learning and stable contextual fear memory but are more efficient in contextual fear discrimination learning, indicative of enhanced pattern separation. Furthermore, mice with more adult-born neurons show greater exploratory behaviour following voluntary exercise. In contrast, increasing adult hippocampal neurogenesis does not produce an anxiolytic- or antidepressant-like behavioral response.

Conclusions: Our findings suggest that strategies designed to specifically increase adult hippocampal neurogenesis are likely to have pro-cognitive effects associated with improved pattern separation, but may not be sufficient to enhance mood.
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167. Chromatin Modification in Psychiatric Disease: Histone Deacetylase Inhibitors Differentially Affect Acetylation and Behavior in Mouse Models

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Background: Evidence from animal models and patient studies suggests that chromatin modification, including histone acetylation and methylation, plays a role in disease etiology and mechanisms underlying treatment of neuropsychiatric disease. Notably, treatment with broad-acting histone deacetylase inhibitors (HDACi) that increase histone acetylation have antidepressant-like effects in mouse models of behavioral despair (Schroeder et al., 2007) and social defeat (Covington et al., 2009). HDAC inhibition may also play a role in valproate treatment of bipolar disorder. Selective regulation of histone acetylation may prove a viable clinical treatment, presuming decreased toxicity-associated side effects compared to nonspecific HDACi compounds. We are examining selective HDACi in rodent behavioral models of mood disorders and assessing chromatin and gene expression changes to distinguish mechanistic underpinnings.
Methods: HDACi with differing selectivity were tested in C57BL/6J mice for attenuation of behaviors modeling affective disorders. Histone H2B, H3 and H4 acetylation and H3 methylation were assayed in brain using western blotting and immunohistochemistry following acute and chronic HDACi treatment.
Results: HDACi treatment modulated affective behavior and increased levels of a limited set of histone modifications in brain. These effects varied by brain region, histone modification, and HDAC inhibition, and were associated with unique behavioral response profiles.
Conclusions: Collectively, these results suggest that selective HDAC inhibition has heterogeneous effects in brain and may underlie distinct behavioral responses. Future experiments examining additional histone modification and gene expression changes will address differences between selective compounds with higher resolution and will provide insight into the basis for the behavioral impact of chromatin modification.
Supported by Stanley Medical Research Institute

168. Magnetic Resonance Imaging of Whole, Anterior and Posterior Hippocampal Volumes in Behaviorally Depressed Cynomolgus Macaques

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Background: Meta-analyses suggest that hippocampal (HC) volume measured via MRI is reduced bilaterally in depressed patients. The HC is functionally differentiated along its anterior-posterior axis such that the anterior HC is associated with emotional functioning. Human studies are complicated by subject heterogeneity in characteristics that affect HC volume, and few report separate measurement of anterior HC. We recently reported an average 15.4% volume reduction *post mortem* in the anterior HC of behaviorally depressed monkeys.
Methods: To confirm these findings *in vivo*, we used MRI to measure whole, anterior, and posterior HC volumes in a matched sample of adult female cynomolgus macaques characterized for behavioral depression (n=6 depressed, 6 nondepressed). High resolution structural MRIs were acquired using a 3 Tesla GE scanner, and T1-weighted images were converted to ANALYZE format. Using MRIcro, HC regions of interest (ROIs) were manually segmented on each 2D slice of all planar acquisitions. HC volumes were normalized to whole brain volumes within subjects to correct for intersubject variation in head size.
Results: Whole, anterior and posterior volumes of both left and right HC were all significantly smaller in depressed compared to nondepressed animals (all $p<0.05$). No effects of laterality were observed.
Conclusions: The observation of smaller HC volume in depressed monkeys is compelling because characteristics known to affect HC volume that vary in human studies are either controlled or absent. These results support our previous observation that reduced HC volume is associated with depressive behavior in female cynomolgus macaques.
Supported by Martin & Sharleen Cohen Foundation for Biomedical Research

169. Expression Levels of NF-kappaB p65 and Sirtuin6 in Prefrontal Cortex Area 10 of subjects with Major Depressive Disorder

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Background: The mammalian family of sirtuins (SIRT1-7) which are also referred to as class III histone deacetylases (HDACs) have been implicated in a wide variety of cellular functions including inflammation and stress responses. SIRT6 is known primarily as a mono-ADP-ribosyl transferase and over-expression of SIRT6 promotes neuronal apoptosis. Proinflammatory stimuli and stress conditions rapidly activate the transcription factor NF-κB, which subsequently induces transcription from several genes, including those encoding inflammatory cytokines. Recently it was demonstrated that SIRT6 deacetylates histone H3 lysine 9 (H3K9) at the NF-κB gene promoter and attenuates NF-κB signaling. Given the evidence of stressors and proinflammatory cytokines in the pathophysiology of depression, it is possible that these proteins may be altered in subjects with major depressive disorder (MDD).
Methods: Western immunoblotting was used to quantify SIRT6 and NF-κB RELA p65 protein levels in nuclear fraction homogenates of prefrontal cortex (PFC, BA 10) from 12 female and 12 male MDD subjects and equal numbers of gender-matched control subjects.
Results: : No significant differences were observed in SIRT6 or NF-κB protein levels in the PFC of female or male subjects with MDD relative to matched control subjects. Although a trend appeared for elevated SIRT6 levels in the PFC of women with MDD ($p=.07$).
Conclusions: SIRT6 or NF-κB proteins in BA10 of the PFC do not appear to play a significant role in the pathophysiology of major depression. However given the unique cellular functions of these proteins and the multiple isoforms, further investigation is warranted to understand the neuronal functions of these proteins.
Supported by Public Health Service Grants P20 RR17701

170. Synaptosomal Cholesterol and Phospholipid Characterisation in Suicide Completers

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Background: Low serum cholesterol has been consistently implicated in suicide and suicidal behaviour. Understanding of brain cholesterol, especially cholesterol turnover, is not yet clearly understood. It is known that cholesterol and phospholipid levels in membranes are dynamic and composition in synaptosomal membranes in particular can have an impact on cell signalling. The objective of this study was to determine if differences exist in synaptosomal cholesterol and phospholipid levels between suicide completers and controls.
Methods: Fresh (un-fixed, un-frozen) brain tissue was obtained from suicide completers and a non-psychiatric control population at the time of brain dissection from the Quebec Suicide Brain Bank. Synaptosomes were isolated by density gradient centrifugation. Electron microscopy was used to confirm isolation of synaptosomes. Synaptosome associated protein 25 kDa (SNAP 25) was measured by western blotting and used to determine synaptosomal enrichment. Cholesterol and total phospholipids were measured using enzymatic assays.
Results: A preliminary sample of n=3 suicide completers revealed by electron microscopy presence of some intact synaptosomes. Western blotting revealed an enrichment of SNAP25 in the synaptosomal fraction (SYN) compare to the total brain homogenate (TBH). Cholesterol was 2.5±1.3 and 1.2±0.1 mg/ml, while total phospholipids were 1.9±0.4 and 1.2±0.1 mg/ml, for the SYN and TBH fractions respectively.
Conclusions: With the targeted sample size of n=15 per group, this study will provide information on the composition of synaptosomes in the brains of suicide completers and controls and insight into whether deregulations of synaptosomal lipid turnover in brain cells of suicide completers may exist.
Supported by FRSQ

171. Reduced Glutathione Levels in Post-Mortem Prefrontal Cortex from Mood Disorder Patients

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Background: Glutathione is the body's major free radical scavenger. Diminished glutathione levels elevate cellular vulnerability toward oxidative stress; characterized by accumulating reactive oxygen species. Accruing data suggest that oxidative stress underlies the pathophysiology of bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SCZ). The purpose of this study is to (1) measure levels of oxidized and reduced glutathione; (2) analyze the synthetic and utilization enzymes for glutathione.
Methods: Post-mortem prefrontal cortex from individuals with BD, MDD, SCZ, and from non-psychiatric comparison controls were provided by the Stanley Foundation Neuropathology Consortium. We utilized an enzymatic recycling methodology for the quantitative determination of oxidized and reduced levels of glutathione. To examine glutathione synthesis, we performed Western blot analyses for the rate-limiting catalytic subunit of glutamate-cysteine ligase. To determine the use of glutathione, we measured via Western blot analyses: glutathione reductase, glutathione peroxidase-1, and glutathione s-transferases mu-1 and pi.
Results: The levels of reduced, oxidized, and total glutathione were significantly decreased in all psychiatric conditions as compared against control. Though the levels of glutamate-cysteine ligase were unaltered in any of these disorders, the levels of glutathione reductase, peroxidase-1, and s-transferase mu-1 were significantly reduced in MDD and SCZ as compared to control subjects.
Conclusions: These findings indicate that glutathione levels are reduced in psychiatric illness and these decreases are due to glutathione usage and not hindered synthesis. These results suggest that psychiatric patients may benefit from antioxidant treatments which increase brain glutathione levels.
Supported by CIHR & Stanley Foundation

172. Levels of Several ERK Pathway Proteins and PDE4 are Altered in Postmortem Frontal Cortex of Individuals with Mood Disorders

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Background: The extracellular-regulated protein kinase (ERK) and cAMP-PKA pathways are key signaling systems for neuronal structure and functional plasticity. The pathways cross talk with each other and converge at several common downstream molecules such as CREB. Both systems are tartgets for treatment with mood stabilizers and antidepressants, and both pathways are involved in behavioral actions in animal paradigms for major depression disorder (MDD) and bipolar disorder (BD). We have investigated the possible alterations of these pathways in human postmortem brain cingulate cortical tissues as compared to normal control subjects.
Methods: Postmortem cingulate cortical tisuue of control, MDD or BD subjects were obtained from the Stanley Foundation Brain Bank. Immunoblotting teniques were used to measure levels of proteins in the ERK pathway and of cyclic nucleotide phosphodiesterase 4 (PDE4), an enzyme that may turn off PKA signaling.
Results: Levels of most measured protein members of the ERK pathway were lower (levels varied across groups) in individuals with psychiatric disorders than controls. Levels of PDE4 B and D were significantly higher in the tissue from individuals with MDD than in those from non-psychiatric controls.
Conclusions: Our results are consistent with a hypothetic role of the ERK pathway in the development of some psychiatric illnesses. Moreover, increased levels of PDE4 protein expression would result in reduced PKA activity, and suggests (besides of its adding effects) an important role in the pathophysiology of mood disorders, providing rational approaches for new therapeutic avenues. Disfunctional ERK and cAMP-PKA pathways are potential pathological contributors of MDD and BD.
Supported by IRP NIMH

173. An In-Vitro Model System to Study rTMS Effects on Cell Signaling

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Background: As a noninvasive neurostimulatory technique, repetitive transcranial magnetic stimulation (rTMS) constitutes a relevant non-pharmacological treatment for depression. Preclinical research indicates that elevation of cAMP, activation of protein Kinase A and subsequent cAMP-responsive element binding protein (CREB) phosphorylation play an important role in mediating the cellular response to antidepressant psychopharmacotherapy. By contrast, little is known about biological mechanisms mediating the antidepressant effects of rTMS. Here, we describe a cellular model system to study effects of rTMS on cell signaling in vitro.
Methods: Human SH-SY5Y neuroblastoma cells were differentiated into neurons with retinoic acid (RA) for 1 week and then exposed to serum free culture medium for 24 h preceding rTMS (1500 pulses, 5 Hz, 30 min.). Drugs were applied 1 h prior to stimulation. Intracellular cAMP and pCREB levels were analyzed using ELISA and Western blot analysis, respectively.

Results: Stimulation resulted in immediate elevations of intracellular cAMP levels and subsequently led to a significant increase in activated transcription factor CREB (pCREB) compared to sham-treated cells. Co-administration of the anesthetic ketamine at 1 μM did not alter the observed effects, whereas lithium (2 mM), a substance known for its cognitive side effects in neurostimulatory treatments, attenuated cAMP and pCREB elevations.
Conclusions: Both pharmacological and neurostimulatory interventions may work through common molecular mechanisms. While potential antidepressant signaling pathways have been identified for pharmacological treatments, this in-vitro study demonstrates similar effects of rTMS for the same canonical pathways, providing a model to further investigate e.g possible pharmacological interactions with rTMS interventions.

174. Chronic Fluoxetine Treatment Differentially Regulates Freud-1 and NUDR in the Rat Prefrontal Cortex

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Background: Alterations in the levels of brain serotonin is thought to be involved in the pathophysiology of major depressive disorder (MDD). The serotonin-related transcription factors Freud-1(five prime repressor element under dual repression) and NUDR/Deaf-1 (nuclear deformed epidermal autoregulatory factor) NUDR function as transcriptional repressors of the 5HT1A receptor, an important player in the mechanism of antidepressant action. There is evidence that both factors are reduced in the prefrontal cortex of subjects with MDD. Therefore, the present study was designed to determine if these two factors are targets of the selective serotonin reuptake inhibitor, fluoxetine.
Methods: Adult male Sprague-Dawley rats were injected with 5 mg/kg fluoxetine for 21 days and sacrificed the following day. The prefrontal cortex was dissected from each brain for analyses of mRNA changes using quantitative real-time polymerase chain reaction. Messenger RNA changes were calculated using the ratio between the copy numbers of gene products to GADPH levels.
Results: Messenger RNA levels for Freud-1 were significantly decreased while that of NUDR tended towards an increase but was not significant. Fluoxetine treated rats showed a significant reduction in body weight compared to control rats injected with saline.
Conclusions: Our results tend to suggest that both transcription factors may be involved in the mechanism of antidepressant action specifically as it relates to the selective serotonin reuptake inhibitor fluoxetine. More importantly they could serve as targets for the design of more effective antidepressants.
Supported by P20 RR 017701

175. Differential Glucocorticoid Receptor Expression in the Brain of Suicide Completers with a History of Childhood Abuse

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Background: Childhood abuse has been shown to alter HPA axis and increase the risk of suicide. Lower glucocorticoid receptor (GR) expression level has been associated with increased DNA methylation in the promoter of the GR_{1F} variant in the hippocampus of suicide completers with a history of childhood abuse as compared to controls. In this study, we looked at the expression of other GR splice variants and compared promoter methylation levels in controls and suicide completers with and without a history of childhood abuse.
Methods: A total of 65 subjects (27 abused suicides, 17 nonabused suicides, 21 controls) were included in the analyses. Expression levels of GR total, 1B, 1Cs, 1D, 1F and 1H variants were quantified using quantitative RT-PCR in post-mortem hippocampus and cingulate gyrus (BA 24). Promoter methylation levels were assessed by pyrosequencing.
Results: The expression of GR variants was generally decreased in the hippocampus and cingulate gyrus of abused suicide completers compared to nonabused suicide completers and CTRL in accordance with a global increased methylation level in their promoter regions.
Conclusions: These findings suggest that early life events interfere with the expression of GR variants in the hippocampus and cingulate gyrus of suicide completers probably by increasing DNA methylation in their promoter regions.
Supported by CIHR

176. Fluoxetine Treatment Does Not Alter Density or Size of CNPase-Immunoreactive Oligodendrocytes in Prefrontal White Matter in Rhesus Monkeys

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Background: Diffusion tensor imaging (DTI) studies in patients with major depressive disorder (MDD) consistently report alterations in axonal integrity in the ventro-medial prefrontal white matter (vmPFC-WM). Our recent postmortem analysis of CNPase-immunoreactive (CNPase-IR) oligodendrocytes in the vmPFC-WM, revealed a 56% increase in the size of oligodendrocytic cell bodies in MDD subjects as compared to non-psychiatric control subjects. However, it could be argued that antidepressant treatment in some of the MDD subjects accounts for the increase in cell body size. Here we tested the hypothesis that long-term treatment of Rhesus monkeys with the antidepressant fluoxetine does not affect the density or size of WM oligodendrocytes.
Methods: Estimation of cell packing density and cell body size of CNPase-IR oligodendrocytes was performed in tissue sections from the vmPFC-WM of 6 Rhesus monkeys treated with fluoxetine (3 mg/kg) p.o., for 39 weeks and 6 monkey treated with vehicle (all male, matched for age, and 5-HT transporter genotype polymorphism) using Stereoinvestigator software.
Results: Neither density nor size of oligodendrocytes was different between monkeys treated with fluoxetine and those treated with vehicle. This is in contrast to significant increases in the size of CNPase-IR oligodendrocytes found in the same prefrontal white matter region of human subjects with MDD as compared to control.
Conclusions: The lack of differences in the density and size of oligodendrocytes in the prefrontal white matter between antidepressant-treated and untreated animals suggests that enlargement in oligodendrocytic cell bodies observed in depressed subjects is not due to antidepressant treatment.
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177. Gene Expression of Estrogen Receptor α and Serotonin Transporter in Women with Premenstrual Syndrome and Premenstrual Dysphoric Disorder

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Background: Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) are associated with intense psychological and physical discomfort. While little is known regarding the pathophysiology of PMS/PMDD, recent studies have suggested that an interaction between estrogen and serotonin transmission may be involved. Here we compare the mRNA expression of estrogen receptor alpha (ER-alpha) and the serotonin transporter (SERT) in leukocytes of women with moderate to severe PMS/PMDD, as compared to those with mild or no PMS symptoms.
Methods: Forty two medication-free women were assessed using the Premenstrual Symptoms Screening Tool (PSST) and the 2-month prospective Daily Record of Severity of Problems (DRSP). Women were grouped in 2 categories: mild/no PMS (n=24) and moderate to severe PMS/PMDD (n=18) according to the PSST. Blood was sampled during both the follicular and luteal phases of the menstrual cycle and quantitative real-time polymerase chain reaction was used to measure gene expression using primer-probe sets for ER-alpha and SERT.
Results: There were no differences in ER-alpha or SERT mRNA between women with moderate to severe PMS/PMDD compared to those with mild/no PMS symptoms (all p>0.05). However, the fluctuation (delta) of SERT mRNA between follicular and luteal phases was positively correlated (r_p=0.45; p=0.04) with the fluctuation (delta) of the 4 core symptoms of PMDD (irritability, depression, anxiety and mood swings).
Conclusions: While this study does not support that changes in ER-alpha mRNA are associated with PMS/PMDD, an increase in SERT mRNA appears to be associated with more intense emotional disturbance during the premenstrual period.
Supported by McMaster Integrative Neuroscience Discovery and Study

178. Functional Analysis of microRNA Expression Profiles in Brain Tissue from Suicide Completers

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Background: TrkB-T1 is a truncated receptor of BDNF which does not have any tyrosine kinase domain. This isoform is highly expressed in astrocytes and regulates BDNF-evoked calcium signals. Previous studies by our group indicate that a subgroup of suicide completers have low expression levels of TrkB-T1. We also evidence epigenetic modifications in TrkB-T1 promoter which partially explain TrkB-T1 low expression level in brain tissue from suicide completers.
The general aim of this study was to investigate microRNAs which could be responsible for TrkB-T1 decrease.
Methods: microRNA microarray studies comparing low TrkB-T1 expressor suicides to normal TrkB-T1 expressor controls were performed. Statistical correction was applied for multiple testing. We used real time PCR in order to validate differentially expressed microRNA results.
Bioinformatic analyses using applications available on the web were performed to determine which sequences could be bound by differentially expressed microRNAs.
Results: After statistical correction for multiple testing, two microRNAs (Hsa-miR-185* and Hsa-miR-491-3p) were found to be differentially expressed. These results were consistent with RT-PCR findings, showing a strong correlation with microarray results.
Bioinformatic analysis confirmed that there might be a link between these two differentially expressed microRNAs and low TrkB-T1 expression level in human brain.
Conclusions: Modulation of microRNA expression in human brain may play a role in suicidal behaviour.
Supported by CIHR

179. Adolescents with Major Depressive Disorder Exhibit Selective Deficits in Erythrocyte Docosahexaenoic Acid Composition: Dissociation from Antidepressant Medication Effects

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Background: Omega-3 (n-3) fatty acid deficiency may contribute to the pathoaetiology of major depressive disorder (MDD). Adult patients with MDD exhibit deficits in erythrocyte n-3 fatty acids, including docosahexaenoic acid (DHA, 22:6*n*-3). However, it is not known whether MDD in adolescence is also associated with erythrocyte n-3 fatty acid deficits.
Methods: Erythrocytes were collected from male and female adolescent (10-20 years) MDD patients (n=15) and healthy controls (n=18). Erythrocytes were also collected from rats following chronic (30 d) treatment with fluoxetine (FLX, 10 mg/kg/d) to evaluate potential confounding effects of chronic antidepressant exposure. Total erythrocyte fatty acid composition was determined by gas chromatography.
Results: Adolescent MDD patients exhibited significantly lower erythrocyte DHA composition relative to healthy adolescent controls (-33%, p<0.0001), and DHA deficits were similar in male and female MDD patients. The n-3 fatty acids eicosapentaenoic acid (EPA, 20:5*n*-3) and docosapentanoic acid (22:5*n*-3) did not differ between groups. The n-3 index (EPA+DHA) was significantly lower in MDD patients (-32%, p<0.0001). There were no group differences for any n-6 fatty acid, including arachidonic acid (AA, 20:4n-6), and the AA:EPA+DHA ratio was elevated in MDD patients (+30%, p<0.0001). Erythrocyte DHA deficits were similar in antidepressant-treated and drug-free MDD patients, and chronic FLX treatment, resulting in therapeutically-relevant plasma FLX and norfluoxetine concentrations, did not alter rat erythrocyte DHA composition.
Conclusions: These data demonstrate that male and female adolescent MDD patients exhibit significant and selective erythrocyte DHA deficits, and suggest this DHA deficit is not altered following chronic antidepressant exposure.
Supported by Inflammation Research Foundation

180. Blood Vessel Pathology and Alterations in Gene Expression of Angiogenic Factors in the Orbitofrontal Cortex in Major Depression

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Background: Clinical studies indicate a bidirectional link between major depressive disorder (MDD) and cardiovascular disease. Impairment of endothelial function and altered expression of angiogenic factors may contribute to cerebrovascular pathology in depression. However, the microscopic integrity of cerebral vessels and angiogenic gene expression has not yet been investigated in MDD.
Methods: Postmortem brain tissue dissected from the orbitofrontal cortex (ORB) gray and white matter was analyzed in 8 pairs of MDD and control subjects. The density and size of blood vessels were measured in sections stained by double immuno-fluorescent-histochemistry for von Willebrand factor (vWF), a functional marker of endothelial cells, and collagen, a structural marker of vascular walls. Quantitative PCR analysis was applied to examine relative gene expression levels of vWF and vascular endothelial growth factor (VEGF). Western blotting was used to determine VEGF protein level.
Results: There was no significant difference between MDD and controls in the density or size of vWF-IR segments of vessels in either gray or white matter of the ORB. However, the area fraction of vWF-immunopositive vessel segments was significantly increased in the ORB gray but not in the white matter in MDD. Moreover, expression of the vWF gene was significantly increased, whereas, VEGF gene expression was decreased in ORB gray matter in MDD. Western blot analysis confirmed reductions in VEGF.
Conclusions: The increased area fraction of vWF-immunopositive vessels together with alterations in the expression of vWF and VEGF gene suggest that these factors may destabilize cortical vessels and endothelial dysfunction in MDD. RR17701
Supported by RR17701

181. Volume, Number of Neurons, and Number of Glia in the Basolateral Amygdala in Major Depressive Disorder: A Postmortem Stereological Study

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Background: The amygdala exhibits hyper-reactivity and impaired functional connectivity with the prefrontal cortex in major depressive disorder (MDD). Postmortem studies have demonstrated an MDD-related decrease in amygdalar glial cell density, and abnormal expression of neurotransmitter receptors and other markers of postsynaptic signaling in the basolateral amygdala. To clarify the anatomic and cellular environment in which these abnormalities occur, we are undertaking the first unbiased stereological analysis of the volume, total number of neurons, and total number of glia in the basolateral amygdala in MDD.
Methods: Postmortem tissues from 11 subjects with unremitted MDD and 10 psychiatrically healthy controls were coded, fixed in formalin, and embedded in celloidin. Forty-micron-thick sections were taken throughout the rostral-caudal extent of the basolateral amygdala, and every tenth section Nissl-stained and mounted on slides for microscopic analysis. The Cavalieri principle and the optical fractionator are used for unbiased stereological estimation of volume and cell numbers respectively.
Results: Results will be presented for volume and cell numbers in the lateral, basal, and accessory basal subnuclei. Preliminary data indicate a significant enlargement of the lateral nucleus in subjects with MDD, but do not indicate MDD-related changes in cell numbers. Implications of the completed results for the role of the amygdala in the pathophysiology of MDD will be discussed.
Conclusions: Identification of subregion-specific amygdalar cellular and volumetric abnormalities in MDD will advance understanding of the underlying neurobiology of major depressive disorder and allow for clearer interpretation of prior research.
Supported by Hearin Foundation, MH67996, RR017701

182. Astrocytic Alterations in Postmortem Hippocampus in Major Depressive Disorder (MDD)

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Background: Astrocytic pathology is implicated in MDD and may account for decreased hippocampal volume in MDD. Astrocyte density was measured in the hippocampus using 3-D cell counting in MDD and control subjects.
Methods: With informed consent from next-of-kin, postmortem hippocampal tissues were collected from 17 individuals with MDD and 17 normal controls. All subjects were diagnosed retrospectively using the SCID. Three 40 µm sections from the body of hippocampus per subject were immunostained for glial fibrillary acidic protein (GFAP), a marker of activated astrocytes. Hippocampal subfields were assessed for GFAP-immunoreactive (-ir) area fraction and astrocyte density.
Results: In MDD, the ratio of astrocytes to pyramidal neurons significantly increased with age in CA1 and CA2/3 but decreased with age in hilus. After adjusting for age as a covariate, astrocyte density in hilus alone is significantly decreased in MDD vs. controls. Astrocyte density in the hilus was significantly lower in depressed subjects without an antidepressant prescription compared to both those with a prescription and controls. No significant differences in GFAP-ir area fraction were noted between MDD and Controls in CA1, CA2/3, or dentate gyrus.
Conclusions: Astrocyte contribution to neuronal function in the hilus may be compromised in MDD. Interestingly, antidepressant therapy appears to restore astrocyte density to control levels in the hilus. As the hilus plays a critical role in hippocampal circuitry, alterations in astrocyte density in the hilus in MDD suggests this structure may be a key site underlying the pathophysiology of MDD and its treatment with antidepressant drugs. *MH67996, RR017701*
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183. Tumor Necrosis Factor-alpha Enhanced AMPA-Containing Synaptogenesis In The Central Nervous System

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Background: Cytokines are small proteins discovered in the immune system for cellular activation and cell-to-cell communication. Recent studies demonstrate that cytokines modulate synaptic plasticity and neuroprotection in the central nervous system. TNFα, a cytokine secreted from glial cells in the brain, regulates neuronal AMPA receptor trafficking and neuroplasticity. However, the direct effect of TNFα on synaptogenesis remains unclear.
Methods: After TNFα treatment, double immunostaining with anti-PSD95 and anti-GluR1 were performed with the hippocampal neurons. Electrophysiological studies were also conducted to confirm the data functionally. In vivo studies were undertaken to determine the TNFα effect in vivo.
Results: We found that treatment with TNFα at low dose (6 pM or 60 pM) for 1 day significantly increased the number of synapses and co-localization efficiency of GluR1 and PSD95. This effect was sustained up to 3 days. However, high dose (600 pM) of TNFα significantly down-regulated the number of synapses and co-localization efficiency of GluR1 and PSD95. These data were confirmed by electrophysiological studies showing that TNFα treatment (60 pM) for 1 day significantly enhanced the frequency of miniature excitatory postsynaptic currents (mEPSC) in the hippocampal neurons. The inhibitor of TNFα receptor TNFR1, significantly reduced the effect of TNFα (60 pM) on synaptogenesis, suggesting a TNFR1-dependent mechanism. Immunohistochemistry studies are being undertaken to determine the number of synapses in the hippocampal CA1 striatum region in vivo after TNFα treatment.
Conclusions: Together, these findings provide novel evidence that glial-derived TNFα promotes AMPA-containing synaptogenesis, which might play a crucial role during traumatic brain damage, inflammation and various psychiatric conditions.
Supported by NIH

184. Daily Left Prefrontal TMS for Major Depression: A Sham-Controlled Multi-Site Randomized Trial (NIH Optimization of TMS for Depression Study, OPT-TMS)

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Background: Daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) has been studied as a potential treatment for depression, but prior work had mixed outcomes and failed to mask sham conditions adequately.
Methods: Medication-resistant patients with unipolar, non-psychotic, major depressive disorder who were currently antidepressant-free were randomized to receive either active or sham rTMS in a multi-site, duration-adaptive design - with 3 weeks of daily weekday treatment followed by continued blinded treatment for up to another 3 weeks in improvers. rTMS was delivered to the left prefrontal cortex at 120% motor threshold, 10 Hz, 4 s train duration, for 37.5 min with a figure-eight solid core coil. Sham rTMS used a similar coil with a metal insert, blocking the magnetic field, and scalp electrodes that delivered matched somatosensory sensations. In the intent-to-treat sample (n=190) remission rates were compared for the two treatment arms using logistic regression and controlling for site, treatment resistance, age and duration of current depressive episode.
Results: Patients, treaters, and raters were effectively masked. The primary efficacy analysis revealed a significant effect of treatment (p=0.015) on the proportion of remitters (14% active rTMS, 5% sham). The odds for attaining remission were 4.2 times greater with active rTMS than sham (95% confidence interval, 1.3 - 13.2). The number needed to treat was 12. Most remitters had low antidepressant treatment resistance. 29.9% of patients remitted in an open-label follow-up phase with active rTMS.
Conclusions: Daily left prefrontal rTMS as monotherapy produced clinically meaningful antidepressant effects greater than sham.
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185. Randomized Trial of Unilateral and Bilateral Prefrontal Cortex Transcranial Magnetic Stimulation in Treatment Resistant Major Depression

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Background: While several studies have reported that repetitive transcranial magnetic stimulation treatment (rTMS) has demonstrable efficacy in patients

with depression, the parameters needed to optimize therapeutic efficacy remain unclear. To this end we compared the efficacy of low frequency right rTMS to the dorsolateral prefrontal cortex (DLPFC) compared to two forms of bilateral rTMS to the DLPFC: (1) sequential low frequency right followed by high-frequency left sided rTMS and (2) sequential low frequency rTMS to both hemispheres.
Methods: 219 patients with treatment resistant depression were randomised to a four week course of rTMS applied with one of the three treatment conditions. Outcomes were assessed with standard rating scales.
Results: Overall slightly greater than 50% of the patients achieved clinical response criteria. There was no substantial difference in response between the unilateral and bilateral treatment groups. Successful response to rTMS was predicted by a greater degree of baseline depression severity.
Conclusions: There is no substantial difference in efficacy between unilateral right sided rTMS and the two forms of bilateral rTMS assessed in the study. Further, our results call into question the specificity between frequency and laterality and rTMS response.
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186. Innovative Depression Treatments: Magnetic Seizure Therapy

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Background: Electroconvulsive therapy (ECT) remains the only established therapy for the large percentage of patients with depression who fail to respond to standard treatments. It is commonly used but has substantial problems including the occurrence of cognitive side effects that are often highly distressing for patients. One highly promising potential alternative is Magnetic Seizure Therapy (MST).
Methods: An open label trial of 100 Hz MST is underway in 15 patients with depression referred for ECT. Extensive pre and post psychopathology and neurocognitive assessments are conducted in order to investigate the efficacy and side-effect profile of MST. Patients also undergo pre and post treatment positron emission tomography (PET) scans using radio-labelled (F18) fludeoxyglucose to assess changes in resting brain metabolism. A description of the process of MST, the program and the first patient treated in Australia will be presented.
Results: The first patient treated in Australia underwent MST for treatment resistant depression in October 2009. The patient no longer met criteria for a major depressive episode following eight MST treatments and has remained in remission at evaluations to date. She did not experience any disorientation following treatments and her neurocognitive assessments revealed no apparent MST related cognitive impairment.
Conclusions: This finding provides us with considerable impetus to continue to investigate the use of MST in treatment resistant depression. Should MST be shown to have similar efficacy to ECT but with reduced side-effects, it is envisioned that it could rapidly replace ECT in clinical practice throughout Australia and indeed internationally with substantial ongoing benefits to patients.
Supported by beyondblue Victorian Centre of Reseach Excellence; National Health and Medical Research Council

187. Seizure Expression of Magnetic Seizure Therapy in Depression

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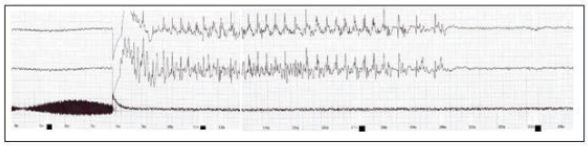
Background: Depression is the most prevalent and probably one of the most disabling of psychiatric disorders in adults. Despite adequate treatment, up to 70% of depressed patients have residual symptoms, and 20% or more may show limited response even with the most aggressive therapies. Magnetic seizure therapy (MST) is a new form of convulsive therapy with more focal seizure induction. Previous studies suggest that MST-induced seizures differ from seizures induced by Electroconvulsive therapy (ECT). The current study was designed to examine and compare the seizure expression in MST and ECT.
Methods: Six patients suffering from a treatment-resistant depression (TRD) were non-responders in a full course of 12 MST sessions. Therefore, 12 treatments of ECT were conducted subsequently. Seizures were elicited under general anesthesia. We observed tonico-clonical motor activity in the cuffed leg, and in addition we recorded ictal synchronization via bipolar, frontal-mastoid scalp EEG.
Results: In most ECT and MST sessions, typical ictal patterns consisting in high-amplitude synchronized theta activity were observed. Furthermore, no clear differences in electroencephalogram (EEG) activity between ECT and MST were observed regarding the ictal activity, especially concerning postictal suppression (see figure).
Conclusions: In contrast to previous studies, we demonstrate comparable seizure expression in MST and ECT, especially in ictal activity and postictal suppression in EEG. This is in contrast to previous studies.



MST seizure expression in EEG.

Supported by MagVenture, Denmark

188. Complementary Use of Tai Chi Improves Resilience, Quality of Life, and Cognitive Function in Depressed Older Adults

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Background: Complementary mind-body interventions can improve partial response to antidepressants via stress-reduction, improved physical functioning, increased socialization, and reduced risks of polypharmacy. This is the first randomized trial of Tai-Chi-Chih used to treat geriatric depression.
Methods: 112 older adults with major depression aged 60 years and older were recruited and treated with 10 mg of escitalopram for the first six weeks. Seventy partial responders to escitalopram continued to receive 10 mg of escitalopram a day and were randomly assigned to 10 weeks of either complementary intervention using: 1.Tai Chi Chih for 2 hours per week; or 2. Health Education Program for 2 hours per week. All participants received comprehensive evaluations of depression, anxiety, resilience, health-related quality of life, and cognition.
Results: Both Tai Chi (TC) and Health education (HE) participants

demonstrated comparable improvement in the severity of depression (mean Hamilton Depression rating scale scores of 6.0 in both groups; p=0.99). However, subjects in the Tai Chi group demonstrated significantly greater improvement in resilience (mean score of 70.2 vs. 65 in the HE group; p<0.05), health-related quality of life (SF-36 scores mean wellbeing scale scores of 80 versus 66; p<0.05), and measures of executive cognitive function (Strop mean errors scores of 0.03 compared to 0.4 errors in the HE group, p<0.05)

Conclusions: Complementary use of mind-body exercise combined with standard antidepressants may provide additional improvement in clinical outcomes of geriatric depression such as resilience, quality of life and cognitive function.

Supported by NCCAM

189. Early Effects of Electroconvulsive Therapy (ECT) on Sleep Architecture in Major Depression

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Background: Many sleep abnormalities are evident in Major Depressive Disorder (MDD), notably short REM latency, disrupted slow wave sleep (SWS), and reduced amplitude and/or distribution of delta power (SWA) in NREM sleep. Previous studies suggest brain stimulation methods may improve sleep in MDD. The present study evaluated early ECT effects on macro- and micro-architectural measures of sleep.

Methods: Thirteen inpatients with MDD (31 to 77 years) were enrolled in the study. Overnight sleep polysomnography was conducted pre-ECT and after the third ECT on 7/13 patients. In addition, EEG was quantified with power spectral analysis. The amount and distribution of delta in NREM sleep was evaluated.

Results: Sleep measures improved with ECT. SWA in the 1st NREM period increased. The distribution of SWA post-ECT returned to a systematic decline across the night. Light non-restorative stage one sleep decreased significantly and REM latency (high at baseline) normalized (p=.05). Total sleep increased. Sleep latency decreased. Depression symptoms (HAMD17) decreased during this time by an average of 12 points (p<.001).

Conclusions: These findings suggest an improvement in sleep homeostasis with enhanced restorative delta in the first NREM period early in the ECT course. Other measures change in the direction of improved sleep. Our results may offer insight into a putative mechanism of action of ECT, and if correlated with outcome, could be early predictors of response to ECT.

Change in Sleep after Three ECT Treatments (mean±SD)

	Pre-ECT	Post 3rd ECT	p
SWA in 1st NREM (μV2)	269.9 ± 62.7	343.6 ± 64.2	.007
Total sleep (min)	365.6 ± 46.8	399.9 ± 18.4	.09
Sleep Latency (min)	31.2 ± 41.3	14.9 ±15.3	.28
% Stage 1	11.4 ± 5.5	7.2 ± 5.2	.02
REM latency (min)	131.5 ± 72.9	63.9 ± 29.4	.05
% SWS	14.3± 14.7	20.4 ± 17.1	.39
SWS in 1st NREM (min)	20.2 ± 25.2	24 ± 20.3	.80

190. Deep Brain Stimulation (DBS) of the Subgenual Cingulate Gyrus for Treatment Resistant Depression (TRD)

Angela Merkl[1], Gerd-Helge Schneider[2], Andrea Kühn[3], Nicole Bührsch[1], Alexander Abbushi[2], Klaus-Peter Kühl[1], Ion Anghelescu[1], Isabella Heuser[1], Malek Bajbouj[1]

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Background: The selection of the subgenual cingulate gyrus (SCG) for neuromodulation with DBS is based on functional neuroimaging studies in the depressive mood state and normalization of hyperactivity in the SCG following successful antidepressant response. We investigated the use of DBS in SCG in depressive patients.

Methods: Three patients with TRD received open-label DBS. Electrodes (3387, Medtronic) were implanted bilaterally in the SCG region. High frequency stimulation (130Hz, 90 μsec pulse-width, 2,5 -10 Volt, monopolar configuration) was titrated to therapeutic benefit (50% reduction of HDRS-24 scores) and absence of adverse effects. Outcome measures included the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI). Neuropsychological assessment was performed at baseline, 6-, and 12 months.

Results: Patient1: HDRS-24 scores declined from 37 at baseline to 20 at 6 months and to 24 at last follow-up (24 months). BDI scores were 35; 30; and 32, respectively. Patient2: HDRS-24 scores declined from 31 at baseline to 10 at 6 months and 4 after last follow-up at 16 months. BDI (22, 3, and 6). Patient3: HDRS-24 scores declined from 28 at baseline to 26 at 6 months and stayed at 28 at last follow up at 10 months. BDI (46, 40, and 40). Remission rates with the HDRS were 33,3% at 6 months and at last follow-up. The DBS was well-tolerated and did not reduce cognitive functioning.

Conclusions: Deep brain stimulation of the subgenual cingulate gyrus is safe and effective for the treatment of refractory major depression and efficacy rates are in line with previous studies.

Supported by James and Ethel Flinn Grant

191. Relationships of Pre and Postpartum Biological Variables with Depression & Anxiety History and Symptoms, Trauma History and Stressful Life Events: Preliminary Results

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Background: We report findings from an initial cohort of 46 mothers, most low income and Hispanic.

Methods: During home visits at pregnancy wk-36 and postpartum wk-6 and wk-12, psychiatric and trauma history, quantity of stressful life events (SLEs), objective and subjective depression and anxiety ratings, and numerous biological measures were obtained.

Results: 41% of subjects reported a major depression history and over half (53%) had suffered sexual or physical abuse. Depression and anxiety symptoms were moderately correlated with trauma history (r range .27-.39). Respective risks for greater depression and anxiety symptoms during pregnancy were significantly predicted (R^2=.30; R^2=.39) by more lifetime trauma (STB=.43, p=.001; STB=.33, p=.02) and higher late pregnancy 24-hr urine cortisol concentrations (STB=.43, p=.001; STB=.42, P=.003). Risks for greater postpartum depression and anxiety (R^2=.33; R^2=.30) were significantly predicted by higher pregnancy cortisol (STB=.31, p=.02; STB=.30, p=.03)

and more SLEs (STB=.47, p=.0008; STB=.42, p=.002) although only SLEs remained predictive (p=.01, p=.001) after controlling for symptoms during pregnancy. Women with lifetime major depression had significantly lower 24-hr urine oxytocin concentrations (10.7pg/ml+7.5[SD] vs. 16.3pg/ml+8.0, p=.04) at postpartum wk-6 (controlling for breast-feeding) and significantly lower serum TSH concentrations at all time points (p<.03). Mothers with postpartum Edinburgh Postnatal Depression Scale scores ≥ 10 had significantly lower TSH at postpartum wk-6 (p=.004), trends toward lower TSH at pregnancy wk-36 (p=.07) and postpartum wk-12 (p=.11) and a trend toward lower 24-hr urine oxytocin at postpartum wk-6 (p=.09).
Conclusions: Several significant relationships among psychosocial, biological and perinatal mood symptoms are emerging in this on-going study.
Supported by R01MH077838

192. Preliminary Result of the Maintenance Phase of an Open Pilot Trial on rTMS Treatment of Bipolar Depression

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Background: Few studies are published on the efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) for the treatment of bipolar depression (BD). Our pilot trial using 20Hz rTMS on the left dorsal lateral prefrontal cortex (LDLPFC) in medication-resistant (failed >2 medications) BD is positive. An add-on study was conducted hypothesizing maintenance rTMS is feasible and safe.
Methods: Eight adult subjects who reached remission (HAMD21<9) in the acute treatment trial volunteered for maintenance treatments of 20Hz rTMS on the LDLPFC weekly for 4 times and then biweekly for one year with routine medications. If relapsed (HAMD>18), subjects would accept daily boost treatments for 1-2 weeks until remitted and then returned to maintenance. Failure to remit or relapsing >2 times led to dropout. Outcomes were assessed by standard psychological scales.
Results: 1.) No severe adverse events (e.g., seizure or treatment induced mania) occurred. Two cases of mild tolerable headache with continued rTMS and one case of fainting likely relating to fasting. 2.) Five subjects relapsed and four of them reached remission again via boost treatments. One completed 1 year of maintenance. One currently continues maintenance beyond 36 weeks. Six subjects dropped: two relapsed >2 times, two due to physical diseases, one for relocation, and one for unknown reasons.
Conclusions: The preliminary results show that one year extended rTMS maintenance treatment plus medication seems reasonably safe. Individualized maintenance protocol is suggested as some subjects demanded more frequent rTMS. Due to the sample size, placebo effect, and potential bias, further randomized sham-controlled studies are warranted.

193. Face Emotion in Adult Bipolar and Unipolar Depression and Controls

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Mood & Anxiety Disorders Program, National Institute of Mental Health, Bethesda, MD

Background: Previous research indicates that patients with major depressive disorder (MDD) are deficient when labeling face emotions. However, few studies have utilized animated facial stimuli or explored sensitivity to facial expressions. Moreover, limited research is available on facial processing in unipolar versus bipolar depression.
Methods: Participants included 31 medication-free, medically healthy patients with DSM-IV MDD and no current substance use, 20 patients with DSM-IV bipolar disorder in the depressed phase, and 24 never-depressed controls. All participants completed the Emotional Expression Multimorph Task, which presents facial emotions in gradations from neutral to 100% emotional expression (happy, sad, surprise, fear, anger, and disgust). Groups were compared in terms of sensitivity and accuracy in identifying emotions.
Results: Subjects with bipolar depression required a significantly more intense facial expression before first responding (F=3.23, p=.045) and correctly identifying (F=3.86, p=.03) emotions as compared to controls. Patients with MDD had average scores between the other groups but were not significantly different. Group differences were not dependent on the type of emotion. Further, the groups were not significantly different in rates of correctly identifying the emotions (F=7.78, p=.18).
Conclusions: Our findings suggest the nature of emotional processing impairments differs between bipolar depression and controls. Bipolar depressed patients displayed deficits in sensitivity when compared to healthy controls, whereas unipolar depressed patients did not exhibit significant differences from either of these groups in sensitivity or accuracy.
Supported by National Institute of Mental Health, National Institutes of Health

194. Abnormal Temporal Sychronization in Bipolar Disorder as Measured by a Paced Finger Tapping Task

Amanda R. Bolbecker[1,2], Jerillyn J. Kent[1], S. Lee Hong[3], Jennifer K. Forsyth[2], Mallory J. Klaunig[2], Colleen C. Merrill[2], Anantha S. Shekhar[2,4], Alan Breier[2,4], Brian F. O'Donnell[1,2,4], William P. Hetrick[1,2,4]

[1]Psychology, Indiana University, Bloomington, IN, [2]Indiana University School of Medicine, Larue D. Carter Memorial Hospital, Indianapolis, IN, [3]Kinesiology, Indiana University, Bloomington, IN, [4]Psychiatry, Indiana University School of Medicine, Indianapolis, IN

Background: Deficits in the temporal coordination of information processing may underlie cognitive and affective symptoms of bipolar disorder (BD). The cerebellum is involved in perceptual and motor timing and individuals with cerebellar lesions can exhibit timing deficits and mood symptoms that are strikingly similar to cardinal features of BD. Moreover, cerebellar volumetric abnormalities have been reported in BD.
Methods: Paced finger-tapping (FT) tasks rely on the cerebellum and have previously been used to characterize internal timing processes in neuropsychiatric disorders. Participants tapped in time with a paced auditory stimulus (500 ms inter-tap interval), then continued tapping without auditory input while attempting to maintain the same pace. This procedure was followed with the dominant index finger (DI), then with alternating thumbs (AT). Fifty BD patients (31 euthymic, 19 manic) and 50 age-matched healthy controls participated.
Results: In general, BD participants showed greater timing variability relative to controls regardless of pacing stimulus (tone- vs. self-paced) or digit (DI vs. AT) The manic group had the highest variability. Euthymic BD participants tapped significantly faster than healthy controls in tone- and self-paced conditions in the AT task. Finally, decomposition of timing variance into internal clock vs. motor implementation components with a computational model showed significant differences between the BD and control groups on clock variability only, with euthymic BD participants exhibiting the highest clock variability.
Conclusions: These findings support previous suggestions of disturbed cerebellar processing in BD and are concordant with our recent finding of cerebellar-dependent eyeblink conditioning deficits in BD.
Supported by NARSAD

195. Effect of Depression on Gender-Sensitive Cognitive Performance

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[1]Psychology, Wayne State University, Detroit, MI, [2]Psychiatry, University of Michigan, Ann Arbor, MI

Background: In healthy adults, women tend to outperform men in perception of emotion in faces, whereas men tend to outperform women in spatial navigation performance. Prior research in young adults with depression has demonstrated female-specific decrements in facial emotion processing, in which depressed women perform more poorly than healthy control (HC) women, whereas depressed men perform similarly to HC men. The current study evaluated whether gender-specific decrements in depression could be extended to spatial navigation ability, associated with better performance among males.
Methods: 31 depressed adults (17 females; 18-83 years) and 35 HCs (21 females; 20-86 years) completed a computerized Morris Water Maze task (MWM), requiring the use of a joystick to locate a hidden platform over several trials in a virtual pool environment, and a computerized facial emotion perception task (FEPT), requiring classification of emotion in photographs of faces.
Results: Repeated measures ANOVA was conducted, with task (i.e., internal z-scores of FEPT and MWM) as the criterion, gender and depression status as predictors, and age and joystick speed as covariates. A significant interaction was present between task, gender, and depression status ($p < .05$). In the depressed group, females outperformed males in the FEPT ($p < .01$), whereas males outperformed females in the MWM ($p < .05$). In HC's, however, gender differences in performance were non-significant (p's > .43).
Conclusions: Although limited by sample size, current results provide evidence that depression exacerbates gender-disparate cognitive abilities. Results will be explored in relationship to neuroendocrine function (i.e., daytime salivary cortisol).
Supported by Rachel Upjohn Clinical Scholars Award (SLW, SAL); Meader Research Fund for Depression/Genetics/Pain (SAL/ SLW); Psychiatry Research Core (SAL).

196. Social Reasoning Deficits in Subsyndromal Patients with Major Depressive Disorder

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Background: Despite evidence of impairments in social cognition in patients with major depressive disorder (MDD), systematic investigations of empathic and theory of mind (ToM) responding in this population have not been conducted.
Methods: Patients with subsyndromal depressive symptoms and matched controls completed a battery of social cognitive tasks shown previously to rely on cognitive and affective processing resources. These included self-rated empathy questionnaires such as the Interpersonal Reactivity Index (IRI) and Toronto Empathy Questionnaire (TEQ), as well as a complex ToM test consisting of first- and second-order false-belief questions.
Results: Relative to healthy subjects, patients reported reduced levels of Perspective Taking(p<0.01) and elevated levels of Personal Distress on the IRI(p<0.01). Altered cognitive and affective empathic abilities correlated significantly with increased symptom severity(p=0.03), extended illness duration(p=0.01), and reduced psychosocial functioning in family(p=0.05), leisure(p=0.05), and occupational domains(p=0.01). Similarly, reduced levels of empathic responding as assessed by the TEQ(p=0.02) was associated with severity of depression(p=0.03) and various psychosocial domains(p's<0.04). Patients were also impaired on second-order ToM tests(p=0.05) but performed comparably to controls on first-order ToM measures. Similar to the empathy measures, deficits in second-order ToM performance were associated with illness state(p=0.06) and reduced levels of everyday social functioning(p's<0.02).
Conclusions: This study provides preliminary evidence of alterations in ToM and empathic responding in patients with subsyndromal MDD. Illness state, illness burden, and cognitive load may influence social reasoning performance in this population. Poor social functioning may result in part from deficits in social reasoning in patients with MDD.
Supported by NARSAD; OMHF

197. Cardiovascular Autonomic Nervous System Alterations during Emotion Regulation in Subjects at Risk for Psychopathology

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Background: Neuroticism is a personality trait characterized by emotion processing biases and a well established risk factor for emotional disorders. Neuroticism has also been associated with a decreased ability to use adaptive cognitive reappraisal strategies and with alterations in autonomic nervous system function. However, it is unknown whether subjects with high neuroticism present with specific biases in emotion regulation expressed through adaptations in the cardiovascular autonomic nervous system.
Methods: Thirty-three healthy subjects (n=13, highly neurotic) performed an emotion regulation task during which they were instructed to either passively view a series of negative pictures or attempt to down-regulate the affect elicited by the images. During the task an ECG was recorded and HRV was measured by calculation of the high frequency spectrum (HF-HRV).
Results: Subjects with high neuroticism scores showed a decreased HF-HRV during emotion regulation, across both passive viewing and reappraisal conditions, compared to subjects with low neuroticism (dF=1.31, F=4.29, p=.047). This seemed to be driven by highly neurotic subjects being less able to regulate their affective response to negative emotional pictures as expressed by lower cardiovascular function adaptability to the stressful task.
Conclusions: Subjects with personality traits associated with risk for depression and anxiety present a dysregulation of the cardiovascular autonomic system response during exposure to negative emotional stimuli. Further investigation is needed to establish whether difficulties in adopting cognitive reappraisal strategies of negative affect and the correlated decrease in cardiovascular adaptability play a role in making highly neurotic subjects more vulnerable to psychopathology.
Supported by Medical Research Council, UK

198. Older Suicide Attempters Bet on Unlikely Gambles

Luke Clark[1], **Alexandre Y. Dombrovski**[2], Greg J. Siegle[2], Meryl A. Butters[2], Cori L. Shollenberger[2], Barbara J. Sahakian[1], Katalin Szanto[2]

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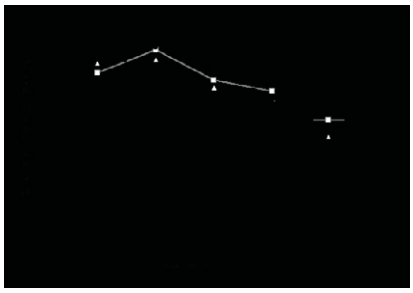
Background: Suicidal behavior is a lethal complication of late-life depression, and recent studies have begun to consider neurocognitive correlates of suicidal behavior. We previously found impaired executive control function in older suicide attempters (Dombrovski 2007). A prominent finding has been of impaired decision-making on the Iowa Gambling Task in euthymic middle-aged suicide attempters (Jollant 2005). This observation converges with neuroimaging findings of alterations within the ventromedial prefrontal cortex, important for risk-sensitive decision-making. We aimed to extend these observations to suicidal elderly.

Methods: We compared performance on the Cambridge Gamble Task (CGT; Rogers 1999) in elderly suicide attempters with major depressive disorder (MDD) (n=25), MDD cases with serious suicidal ideation without an attempt (n=13), MDD cases with no lifetime history of suicidal ideation or attempt (n=35), and non-psychiatric controls (n=22). The CGT assesses probabilistic choice and betting behavior without placing overt demands on learning or working memory.

Results: Suicide attempters more often chose the unlikely gamble, after covarying for group differences in education (F[3,90]=3.05,p=.032), relative to both non-suicidal depressed (Tukey's p=0.02) and depressed controls (Tukey's p=0.01). Attempters and ideators showed moderate slowing (F[3,90]=3.23,p=.026). There were no group differences in betting behavior.

Conclusions: In an uncertain environment, older suicidal attempters seem to make choices that ignore the probability of outcomes. This tendency to bet on unlikely gambles could contribute to a suicidal crisis and may help clinicians identify depressed elders vulnerable to suicidal behavior.



Supported by Medical Research Council (U.K.) and the Wellcome Trust; American Foundation for Suicide Prevention; K23MH086620

199. Older Suicide Attempters Fail to Represent Choice Consequences: Computational Model-Based fMRI Study

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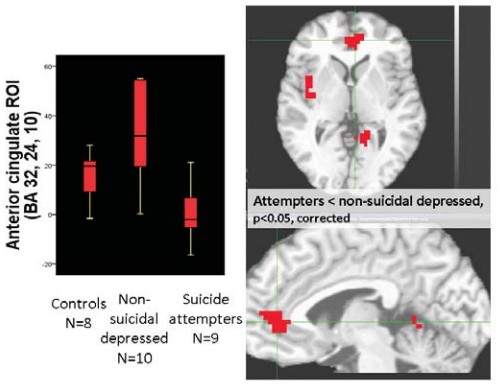
Background: Worldwide, suicide rates peak in old age, and cognitive mechanisms probably play an important role in late-life suicide. Impaired decision-making has been linked to attempted suicide (Jollant, AJP 2005). Older suicide attempters in particular make poor decisions in an uncertain and changing environment, ignoring past experiences and paying excessive attention to the most recent ones (Dombrovski, AJP 2010). Consistent with earlier neuroimaging findings of alterations in the prefrontal and cingulate cortex (Monkul, MolPsych 2008; Jollant, AJP 2008; Oquendo, AGP 2003), we hypothesized that older suicide attempters will show a disrupted representation of choice consequences in these areas.

Methods: We used fMRI to assess brain activity as participants made choices guided by feedback in an uncertain and changing environment (probabilistic reversal learning) in 9 older suicide attempters with major depressive disorder (MDD), 10 non-suicidal depressed elders, and 8 non-psychiatric controls. Using a computational model, we estimated expected value of the best available choice based on each subject's behavior. We mapped the brain representation of value and identified regions that differed between suicide attempters and non-suicidal depressed.

Results: Suicide attempters showed less correspondence between model-estimated value and activity in the anterior cingulate cortex, right insula, posterior cingulate, and left ventrolateral prefrontal cortex, compared to non-suicidal depressed elders.

Conclusions: Failure to represent the consequences of available choices in cingulate and prefrontal cortex may lead to poor decisions and undermine deterrents to suicide in vulnerable depressed elders.



Supported by American Foundation for Suicide Prevention; K23MH086022; K23MH070471

200. Volume of Right Precuneus is Associated with Visual Perspective in Autobiographical Memory: A Voxel-Based Morphometry Study

Maxime Freton[1], Cedric Lemogne[2,3], Loretxu Bergouignan[4], Claudette Boni[5], Philip Gorwood[5,6], **Philippe Fossati**[2,7]

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Background: Acute depression is associated with decreased of 1st person (versus 3rd person) visual perspective in autobiographical memory retrieval. This impairment persists after full clinical remission. 1st person perspective is also decreased in never-depressed subjects presenting vulnerability for depression. Few structural Magnetic Resonance Imaging (MRI) studies have investigated

neural correlates of vulnerability for depression.
This study examined if individual differences in visual perspective may reflect structural variance in specific brain regions, in healthy never-depressed subjects.
Methods: 45 right-handed healthy young adults underwent structural MRI scans and Autobiographical Memory Test (AMT) with an assessment of visual perspective. The differences of regional grey matter volume (GMV) were determined by optimized Voxel-Based Morphometry. The normalisation methods used the most recent DARTEL algorithm.
Results: The region-of-interest analyses, when corrected for multiple comparisons, revealed that the 1st person perspective score during autobiographical memory retrieval positively correlated with the volume of the right precuneus (p = .008) and right parahippocampal gyrus (p = .021). The correlation was significant even after the effects of gender, age and total GMV were taken into account. There was no significant correlation between medial prefrontal volume and the 1st person perspective score.
Conclusions: The results indicate that the visual perspective measured using AMT may have specific neural bases with involvement of precuneus and parahippocampal gyrus. These regions may play a role in the autobiographical memory impairment observed in depression.
Supported by Fondation pour la Recherche Médicale

201. Self-Referential Processing and the Prefrontal Cortex Over the Course of Depression: A Pilot Study

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Background: Depressed patients exhibit cognitive biases, including maladaptive self-focus. In a previous functional magnetic resonance imaging (fMRI) study, we found a unique activation of the dorsal medial prefrontal cortex (MPFC) and dorsolateral prefrontal cortex (DLPFC) during self-referential processing in depressed patients. The aim of this pilot study was to examine whether this activation pattern was stable over the course of depression.
Methods: Sixteen participants (8 depressed inpatients and 8 healthy controls) viewed personality traits during fMRI and judged whether each trait described them or not ('self' condition), or whether it described a generally desirable trait or not ('general' condition). There were 2 scanning sessions with an interval of at least 6 weeks, in which patients received an antidepressant treatment.
Results: All patients improved from session 1 to session 2 and 3 patients achieved remission. Although the activation of the left DLPFC normalized between the 2 sessions, a greater activation of the dorsal MPFC in 'self' versus 'general' condition remained in depressed patients. The 3 patients who achieved remission were those who experienced the greater decrease of the left DLPFC activation in self versus general condition from session 1 to session 2.
Conclusions: The normalization of the left DLPFC activity suggests that antidepressants are associated with a more balanced allocation of cognitive control across self-referential and non self-referential processes. Future studies could examine the relationships between the dorsal MPFC activity in depressed patients and the need to reduce self-focus through CBT to achieve remission and prevent relapse.
Supported by NARSAD

202. Regulatory Focus and Reward Sensitivity: Integrating Social-Cognitive and Affective Neuroscience Perspectives

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Background: Social-cognitive and temperament-based models of reward responsiveness and approach/avoidance motivations are presumed to independently explain individual differences in sensitivity to reward feedback. Regulatory focus theory (RFT) indicates that socialization history combined with features of temperament influence an individual's use of reward information to guide behavior. This study extends the implications of RFT for reward-related learning using a validated signal-detection task as an objective measure of sensitivity to reward feedback. The neurobiological mechanisms governing these behaviors also are explored via common genetic polymorphisms affecting dopaminergic signaling.
Methods: Healthy volunteers completed a probabilistic reward task, where hedonic capacity was operationalized as bias towards choosing the more frequently rewarded stimulus over time. Participants completed self-report measures of regulatory focus, mood, and behavioral activation/inhibition. Saliva samples were collected for genotyping catechol-o-methyltransferase val[158]met.
Results: In analyses with the first 36 participants (anticipated final N=100), individual differences in regulatory focus appear to be correlated with response bias. Behavioral activation strength was not associated with either regulatory focus or task performance. Anhedonic symptoms of depression predicted decreased response bias, as anticipated. Analyses in the complete sample will determine whether anhedonia (a state variable) and regulatory focus (a trait variable) independently predict reward sensitivity, as well as the potential contribution of genetic variability.
Conclusions: This study extends regulatory focus theory by integrating psychological models of self-regulation strategies with neurobiological models of reward processing mechanisms, providing a link between social cognition and affective neuroscience.
Supported by NSF GRFP

203. Bipolar and Unipolar Depression are Distinguished by Patterns of Abnormal Occipital Activity to Happy and Sad Facial Expressions

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Background: Bipolar disorder (BD) is frequently misdiagnosed as unipolar depression (UPD), delaying appropriate treatment and worsening clinical outcome. Mood dysregulation and emotional biases are associated with dysfunction in subcortico-limbic and cortical-prefrontal areas in both disorders. UPD but not BD is linked with aberrant neural activation in extrastriate visual areas. Measures of dysfunction in neural systems supporting emotion processing may help discriminate BD and UPD.
Methods: Using fMRI, neural activity to intense and mild happy and sad, and to neutral faces were measured in two event-related paradigms in 14 depressed BD, 16 depressed UPD and 16 healthy individuals (HI). Using whole-brain analysis (p(uncorrected)<0.001) we first compared depressed BD and UPD individuals, then each patient group to HI.
Results: Within extrastriate visual areas, we observed 1) significantly increased

activation for depressed BD relative to depressed UPD individuals within right middle occipital and lingual gyri for happy faces of all intensities (F(1,83)=13 .08,p(corrected)=0.05); and 2) significantly increased activation for depressed UPD relative to depressed BD individuals within left occipital regions (BA18) for sad faces of all intensities (F(1,83)=14.38,p(corrected)<0.05).
Conclusions: The double dissociation observed within occipital areas in depressed BD and UPD individuals when processing happy and sad faces, respectively, indicates that distinct physiological processes may be associated with both mood disorders. Preferential increases within visual processing areas to sad and happy faces in UPD and BD individuals respectively, reflect emotional biases and impaired interpersonal functioning associated with both disorders. Differential activation within extrastriate visual face processing areas might therefore aid in distinguishing BD from UPD depression.
Supported by MLP: 5ROI MH076971-01; SH: NARSAD

204. Comparison between Depressed Patients and Healthy Controls in Error Refractory Period using the Parametric Go/No-Go Test

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Background: Prior research suggests that inhibitory control dysfunction is present in depressed individuals, including slower set-shifting and interference resolution using the Parametric Go/No-Go (PGNG) task. Newer results show these effects may be related to an s allele of the serotonin transporter (5HTTLPR). We investigated whether a difference in the error refractory period (ERP) might explain these effects of group and 5HTTLPR.
Methods: Twenty-three MDD participants and 26 healthy control subjects were recruited with informed consent and approval of the University of Michigan Medical Center. The groups were screened using SCID_IV and matched in demographics. Participants completed the PGNG task during functional MRI. In assessing errors of commission, we focused specifically on the second (xy, non-repeating) and third (xyz, non-repeating) levels of the task.
Results: A repeated measures ANOVA was conducted including two response times just prior to and after an error of commission (5 RT for trial variable), with group and number of serotonin alleles as independent variables. Preliminary results with 12 HC and 13MDD showed an interaction between group and level of the task (p=.047), group, 5HTTLPR, and level of the task (p=.0001) and trial and group (p = .022). Further analyses will look at the fMRI signature of ERP in MDD compared to HC, by using the time window of the ERP and the magnitude of the post-error RT slowing as regressors.
Conclusions: The present results suggest that the ERP and related error-specific metrics could be fruitfully pursued in understanding the relationship between inhibitory control, depression, and 5HTTLPR.
Supported by PO1 MH 42251, O5 MH 01931, MO1 RR00042,K-23 award

205. Positive Emotional Expression and the Self-Other Boundary in Bipolar Disorder

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Background: Self-concept disturbance is central to the clinical presentation and diagnosis of bipolar disorder. Emotion processing and facial recognition have been shown to be altered in bipolar disorder, however interactions between the two are poorly understood and no studies to date have assessed the impact of emotion upon self-face recognition.
Methods: Subjects with Bipolar I disorder currently euthymic (N=9), and healthy controls (N=11) were photographed in each of three expressions (happy, sad, neutral). These images were morphed in 5% steps with an unfamiliar face of similar age and appearance. Control tasks utilized two unfamiliar controls or shape morphs. In a forced-choice paradigm subjects identified the identity of a counterbalanced randomly presented morph.
Results: 1)There was a differential effect of happy expression wherein it expanded the range of self-recognition in bipolar disorder and constricted it in healthy controls (p<0.02). 2)There was no significant effect of either sad or neutral emotion upon self-other boundary. 3)There were no significant findings on a control shape discrimination task
Conclusions: This is the first study to demonstrate that emotional content impacts upon the boundary at which the self is defined in bipolar disorder. Increasing evidence demonstrate overlap in the neural systems subserving self-related processing and emotion regulation. Those with bipolar disorder have demonstrated altered processing of positive stimuli as compared to controls or those with unipolar depression and this study is evidence toward these alterations impacting upon self-related processing.

206. Autobiographical Memory and Future-Oriented Thinking in Recurrent Major Depressive Disorder

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Background: Autobiographical memory (AM) and future-oriented thinking are thought to rely upon the same underlying neural substrates and cognitive processes. A substantial number of studies reveal overgeneralization, by which AM comprises primarily factual or repeated information in patients with major depressive disorder (MDD). We examined whether this lack of AM specificity in MDD is influenced by participant's mood state (i.e., euthymic versus depressed) at the time of event encoding. Participants were also asked to imagine positive, negative and neutral future events.
Methods: Using the Autobiographical Interview, participants with recurrent MDD and matched controls were asked to recall an event encoded during i) positive ii) negative/depressed and iii) neutral/euthymic mood state. Future-oriented thinking was tested using a modified Crovitz cue word paradigm, where participants had to imagine future events of a positive, negative and neutral valence.
Results: Whereas patients with MDD recalled fewer details of events encoded during positive and euthymic mood states, recall for events encoded during a depressed state was enhanced. Patients imagined less specific and less vivid future events than controls, regardless of emotional valence.
Conclusions: Patients with MDD showed impoverished AM for events encoded during positive and euthymic mood states. Memory for events encoded during a depressed mood state, however, was enhanced in this group. AM contributes to an individual's sense self-identity across time; events encoded during depressed states may be better recalled due to their consistency with self identity in patients with recurrent MDD. Impoverished AM in MDD extends to the ability to envision future events.
Supported by National Scottish Rite Charitable Foundation

207. Reduced Lateral Prefrontal Cortex Activation During an Emotional Working Memory Task in Pediatric Bipolar Disorder

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Background: Studies suggest abnormalities in neural systems underlying voluntary emotion regulation in pediatric bipolar disorder (BD). However, few studies have examined neural activity associated with processes at the interface of cognitive control and emotion. Recent evidence suggests that youth with BD exhibit decreased lateral prefrontal cortical activity associated with modulation of attention to emotion. In this study, we examined differences in neural activation (BOLD) in lateral PFC during an emotional working memory fMRI paradigm in youth with BD-I (BD-I) vs. healthy controls (HC).
Methods: A total of 16 youth, 8 BD-I and 8 age- and sex ratio-matched HC (10-17 years; mean age 14.7 years) completed the Emotional Face N-back (EFNBACK) task during an fMRI scan using a 3T scanner. In this task, subjects were directed to ignore emotional facial expressions (fearful, happy, or neutral) while performing a visual N-back task (0-back, 2-back). Preliminary analyses using SPM5 focused on the lateral PFC as a region-of-interest and the following contrast: fearful vs. neutral face in the 2-back memory load condition.
Results: Relative to HC, BD-I showed significantly reduced activation in dorsolateral PFC (BA 9/46) on the 2-back fearful face vs. neutral face contrast ($p<0.05$, uncorrected). There were no significant differences in accuracy or reaction time.
Conclusions: These preliminary findings indicate that youth with BD show abnormalities in the recruitment of cortical systems implicated in attentional control to emotional information. Additional assessments and analyses are ongoing to replicate these findings in a larger sample and examine effects of illness onset, comorbidity, and medication.
Supported by Klingenstein Foundation; NIMH(MH 059929)

208. Regional Brain Asymmetries during Verbal and Spatial Tasks in Depression with High or Low Trait Anxiety

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Background: Studies of regional hemispheric asymmetries of resting EEG point to relatively less activity (greater alpha) in left frontal and right posterior regions in depression. In contrast, anxiety has been associated with relatively greater right posterior activity, which is thought to reflect arousal and which may offset the characteristic posterior asymmetry in anxious-depressed individuals. However, it is unclear whether these resting EEG asymmetries are also evident during tests of neurocognitive function.
Methods: The present study used matched verbal (Word Finding) and spatial (Dot Localization) tasks to compare task-related EEG alpha asymmetries (13 pairs of electrodes) in depressed patients grouped according to level of trait anxiety. Participants were high (n=14) or low anxiety (n=14) depressed patients and 21 age- and education-matched healthy adults. Behavioral performance and EEG alpha power were recorded for each task.
Results: As predicted, the two patient groups exhibited opposite patterns of task-related regional alpha asymmetries. Greater right than left central-parietal activation was seen in the high-anxiety depressed group during the spatial task, whereas the verbal task elicited greater left than right frontal-central activation in the low-anxiety depressed group. Additionally, low-anxiety depressed patients and controls performed better on the verbal than the spatial task, whereas this performance asymmetry was not found in the high-anxiety depressed group.
Conclusions: These results are consistent with Heller's two-dimensional model of depression and anxiety (1995) and highlight the sensitivity of task-related alpha in discriminating among subgroups of depressed patients differing in trait anxiety.
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209. Obsessive Compulsive Disorder and Executive Cognitive Functions: Correlation to a 18FDG-PET Study

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Background: Obsessive compulsive disorder (OCD) is a severe and disabilities disorder suggested to be related to a dysfunction of the orbitofrontal cortex - striato - thalamo cortical circuit. The aim of this study was to evaluate executive functioning in patients suffering from OCD, and to suggest hypothesises of a physiological model of OCD based on functional imaging data.
Methods: One group of 15 patients with OCD and a 15 healthy control (HC) group took part in the study. The two groups were matched for age, sex and education level. To assess cognitive potential, patients and healthy controls were subjected to the same neuropsychological tests. All subjects were also assessed by 18F-FDG-PET in a resting state.
Statistical analysis was performed with SAS software 9.1 (SAS Institute, Cary, NC, USA) and PET images were analyzed with SPM2 software.
Results: At scores in TMT B and Tower of London, no significant difference was observed between patients and controls regarding the tasks assessing attentional abilities, whereas the time to complete the tasks was always significantly increased in OCD group. No significant difference was observed with other tests.
Hypermetabolism in OCD patients was observed in the left inferior frontal gyrus (Brodman Area (BA) 45) and in the right middle frontal gyrus (BA 9). Hypometabolism in OCD patients was observed in the right ACG (Brodman Area (BA) 31, BA 24), in the left insula (BA 13), and in the left inferior parietal gyrus (BA 40) (uncorrected $p<0.001$).
Conclusions: OCD could not only be explained by a dysfunction of orbito frontal cortex but by a larger region including parietal cortex and dorso lateral prefrontal cortex. These functional imaging results allow us to support the hypothesis of a new physiopathological model of OCD.

210. Are Neurocognitive Complaints Persistent During the Follicular Phase in Women with Premenstrual Syndrome and Premenstrual Dysphoric Disorder?

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Background: Moderate to severe premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) are associated with significant psychological and functioning impairment. Women with PMDD also report changes in neurocognitive processes such as impaired concentration, memory, and motor coordination during late luteal phase. The extent to which deficits in neurocognitive function observed during the luteal phase persist during the follicular phase of the menstrual cycle remains unknown.
Methods: This pilot study investigated differences in neurocognitive performance in the follicular phase of their menstrual cycle between 12 women with moderate to severe PMS/PMDD and 24 women with mild PMS. Participants were clinically assessed using the Premenstrual Symptoms Screening Tool (PSST) and groups were determined based on severity of irritability and degree of impairment.
Results: Preliminary differences between groups were observed on the Finger Tapping Test , a measure of motor speed and control, where women with moderate to severe PMS/PMDD showed increased motor speed compared to women with mild PMS. There was also a trend towards impaired performance on a selective attention task in women with moderate to severe PMS/PMDD. Finally, significant negative correlations were observed between severity of premenstrual core symptoms and accuracy measures of the N-Back task, a measure of selective attention and working memory.
Conclusions: The core symptoms of premenstrual syndrome, namely irritability and anxiety, may contribute to impairment in neurocognitive function across the menstrual cycle. A larger sample to be studied will help elucidate further associations between premenstrual symptoms and subtle changes in neurocognitive performance in this population.

211. Significant Reduction of EEG Alpha Activity and Sensory Alpha Response in Bipolar Patients

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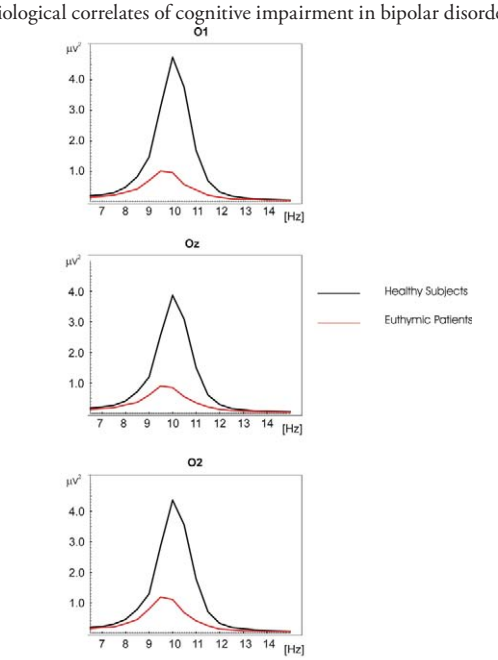
Background: Brain's alpha activity alpha responses belong to major electrical signals that are related to sensory/cognitive signal processing. The present analysis' aims to analyze the spontaneous alpha activity in drug free euthymic bipolar patients.
Methods: Fourteen DSM-IV euthymic bipolar patients and fourteen healthy controls were included in the study. Patients needed to be euthymic at least for 4 weeks and psychotrop free for at least 2 weeks. Spontaneous EEG (4 min eyes closed, 4 min eyes open) and Evoked alpha response upon application of simple visual stimuli were analyzed. EEG was recorded at 30 positions. The digital FFT-based power spectrum analysis was performed for spontaneous eyes closed and eyes open conditions and the response power spectrum was also analyzed for simple visual stimuli.
Results: The ANOVA on alpha responses revealed significant results for groups ($F(1.26) = 7.581$; $p = 0.011$). Post-hoc comparisons showed that spontaneous EEG alpha power of healthy subjects was significantly higher than the spontaneous EEG alpha power of euthymic patients. Furthermore, visual evoked alpha power of healthy subjects was significantly higher than Visual Evoked EEG alpha power of euthymic patients ($F(1.26) = 4,511$; $p = 0.043$).
Conclusions: Decreased alpha activity in spontaneous EEG is an important pathological EEG finding in euthymic bipolar patients. Together with an evident decrease in evoked alpha responses, the findings may lead to a new pathway in search of biological correlates of cognitive impairment in bipolar disorder.



Grand Averages of power spectra of Healthy subjects and Euthymic Patients during eyes closed condition

212. Decrease of Long Distance Gamma (28-48 Hz) Coherence in Euthymic Drug Free Bipolar Patients upon Cognitive Load

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Background: Evoked and Event Related EEG coherences are measures of connectivity between different areas of the brain. Coherent gamma oscillations (30-80 Hz) are critical for cortico-cortical communication and large-scale integration of distributed sets of neural networks. The aim of this study was to investigate long distance gamma (28-48 Hz) coherences under cognitive load in Bipolar Disorder.
Methods: We evaluated gamma coherence in responses to target stimulus

during visual odd-ball paradigm in 15 drug free patients with bipolar I (n=13) or II (n=2) disorder who were euthymic for at least six months in comparison to 15 sex and age matched health controls. Inter-hemispheric F3-F4, T7-T8, TP7-TP8, P3-P4, O1-O2 and intra-hemispheric left (F3-T7, F3-TP7, F3-P3, F3-O1), and right sided (F4-T8, F4-TP8, F4-P4, F4-O2) electrode pairs were included in the analysis. Z scores of the coherence values were analyzed by using Repeated Measures ANOVA, and Mann Whitney U tests.
Results: Patients had lower mean gamma coherence z scores than that of healthy controls at all locations studied. However, the difference was significant at left fronto-anterotemporal (F3-T7, p: 0.019), fronto-posterotemporal (F3-TP7, p: 0,019) and right fronto-posterotemporal (F4-TP8, p: 0.002) locations.
Conclusions: Bipolar patients show decrease in long distance fronto-temporal coherence during a cognitive paradigm, which involves attention and working memory. The results indicate that analysis of gamma is a candidate to determine biological correlates of cognitive impairment.

213. Cognitive, Emotion, and Motor Inhibition in Bipolar Disorder

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Background: Impaired inhibition is one of the more consistent cognitive impairments reported in patients with bipolar disorder. Previous studies have examined performance on cognitive, emotion, and motor inhibition tasks separately but have not examined the relationship between inhibition performance across different task domains (cognitive, emotion, and motor). The present study examined performance and the neural circuitry subserving cognitive, emotion, and motor inhibition in bipolar patients and healthy controls.
Methods: Euthymic bipolar I patients and matched healthy control participants performed a stop-signal task and color-word and emotional Stroop tasks while undergoing fMRI. We calculated between-group differences and within-group correlations for performance and neural response for all three tasks.
Results: Bipolar patients (BP) performed significantly slower across all three tasks and exhibited lower performance accuracy on the color-word and emotional Stroop tasks. Performance on the stop-signal task was not related to performance on either Stroop task; however, performance on the color-word and emotional Stroop tasks were positively correlated for BP and controls. Across all three tasks, controls demonstrated greater dorsolateral and ventrolateral prefrontal cortical and bilateral anterior cingulate activation compared to BP.
Conclusions: Results from the present study are consistent with previous research suggesting that bipolar patients exhibit greater impairment on tasks requiring automatic inhibition. The current study also provides additional evidence for disrupted recruitment of neural regions known to support successful inhibition in patients with bipolar disorder. Further studies are needed to examine the impact of impaired inhibition and neural dysfunction in bipolar disorder.

214. Stress, Limbic Irritability and Nonlinear Heart Rate Dynamics in Unipolar Depressive Patients

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Background: According to recent findings stress represents significant condition in pathophysiology of depression and influences abnormal development in the brain. Repeated stress and cognitive conflict also may determine sensitization, limbic irritability and temporal-limbic epileptic-like activity. Because recent findings indicate that epileptiform processes are related to increased neural chaos, the aim of this study is to find relationship between neural chaos in autonomic responses reflecting brain activity during stress activation and temporal-limbic epileptic-like activity.
Methods: For empirical examination of suggested hypothesis Stroop word-colour test, ECG recording, calculation of chaos indices i.e. largest Lyapunov exponents (LLEs) in nonlinear data analysis and psychometric measures of cognitive, affective and memory symptoms related to temporal-limbic epileptic-like activity called complex partial seizure-like symptoms (LSCL-33, structured interview CPSI), traumatic stress (TSC-40) and depression (BDI-II) in 60 patients with unipolar depression (mean age 33.5) and 50 healthy controls (mean age 32.4) were used.
Results: Significant correlation r=0.59 (p<0.01) between LLEs and LSCL-33, and significant correlation r=0.58 (p<0.01) between LLEs and CPSI found in the depressive patients indicates that degree of chaos in autonomic responses during conflicting Stroop task reflected by LLEs is closely related to limbic irritability. Correlation between LLEs and BDI-II (r=0.35, p<0.01), between LLEs and TSC-40 (r=0.39, p<0.01) were less significant. Similar correlations in healthy controls were not found.
Conclusions: The result are in agreement with findings that epileptiform activity is closely related to neural chaos and potentially might provide explanation of neurobiological mechanisms underlying stress sensitization and predictive marker of anticonvulsant treatment of depression.
Supported by MSM0021620849, 1M06039

215. Traumatic Stress, Dissociation and Limbic Irritability in Patients with Unipolar Depression

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Background: According to recent evidence stressful experiences are related to psychological and neurobiological changes that significantly influence brain functions. Cognitive and emotional dysregulation related to traumatic stress and dissociation is likely linked to deficits in inhibitory functions and increased limbic excitability that may lead to temporo-limbic epileptic-like activity producing psychosensory, affective and memory seizure-like symptoms that may appear in non-epileptic conditions. Because depression is also significantly related to stress, these findings suggest a hypothesis that increased presence of the seizure-like symptoms could be associated with significantly more severe depressive symptoms, symptoms of traumatic stress and dissociative symptoms in unipolar depressive patients.
Methods: With this aim we have assessed seizure-like symptoms, depressive symptoms, symptoms of traumatic stress and dissociation in 113 patients with unipolar depression and 86 healthy controls.
Results: Results of this study indicate that in depressive patients seizure-like symptoms display significant correlation with depression and also with symptoms of dissociation and traumatic stress.
Conclusions: In agreement with recent findings the results suggest that several patients with unipolar depression who have heightened level of the seizure-like symptoms could positively respond to anticonvulsant treatment.
Supported by MSM0021620849, 1M06039

216. APOE Genotype and Bipolar Disorder Cognition

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Background: Apolipoprotein E (*APOE*) has been extensively studied as a risk factor both for sporadic and late onset of familial Alzheimer Disease (AD). The *APOE**3 variant occurs most frequently and is not related to cognitive impairment (CI) or AD risk, while the *4 allele is a well-established risk factor for CI and *2 allele is associated with survival and longevity among older adults. CI in Bipolar Disorder (BD) patients is common and recent data suggest that it may be one of the disease´s endophenotypes. The role of *APOE* genotypes in mood disorder is unclear, as we have controversial results reporting different

associations, frequencies and plasma levels. The objective of this research is to study the association of *APOE* genotype and neurocognitive function in a sample of drug naive young BD type I patients in acute episode, and test the existence of a cognitive endophenotype for BD.
Methods: 25 BD type I symptomatic patients were submitted to an extensive neuropsychological evaluation and genotyped for *APOE*.
Results: The occurrence of *4 was associated with worse performance in a few executive tasks. The present of the *APOE* *3*3 reflected a worse overall cognitive performance. Subjects with allele *2 showed better cognitive performance.
Conclusions: *APOE* genotype in drug naive symptomatic young BD type I could be a useful tool to predict and identify patients with worse cognitive performance.

217. COMT Val158Met and Neurocognitive Function in Bipolar Disorder

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Background: Catechol-0-Methyltransferase (COMT) enzyme catabolizes dopamine (DA) which plays an important role in cognition via the prefrontal cortex. *COMT* single nucleotide polimorphism (SNP) Val158Met (rs4680) has its Met allele reported to increased cognitive activity in the prefrontal cortex. The Val allele is overrepresented in the bipolar subjects and is associated with BD. Only few reports describe the effect this *COMT* variant on Bipolar Disorder (BD). The objective of the current study was to examine the relationship between COMT Val158Met and neuropsychological performance in young drug free bipolar disorder symptomatic patients.
Methods: Drug free symptomatic BD type I patients were submitted to an extensive neuropsychological evaluation and genotyped for COMT Val158Met. Nonparametric tests were used to compare neuropsychological performance between groups.
Results: We found no association between COMT genotype and neuropsychological tasks. However, patient's gender differed on cognitive performance of two memory tasks, with a worst performance in the female group. In the male group, carriers of Val allele performed better in three cognitive tests.
Conclusions: Although the current study found no association between COMT Val158Met and neuropsychological tests results, we found an intriguing difference between gender, polymorphism expression and cognitive performance. Even though our results reflect a partial analysis from a small sample they are important to understand the influence of clinical and neurocognitive characteristics in studies of psychiatric genetics.

218. Conflict Monitoring Dysfunction Underlying the Negative Attentional Bias in Remitted Depressed Patients

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Background: Remitted depressed patients (rMDD) display an attentional bias for negative information. Understanding the specific nature of cognitive control deficits underlying this attentional bias might shed new light on existing models of vulnerability to depression.
Methods: We developed a cued paradigm in which matched groups of rMDD and never depressed controls (ND) responded to the actual or opposite emotion of sad or happy faces, or simply pressed when the face appeared on the screen. In this event related potential study, we used Low Resolution Brain Electromagnetic Tomography (LORETA) to investigate the generators of particular components.
Results: Both groups increased cognitive control during the cue preparation time, demonstrated by enhanced N2 activation localized to the inferior frontal gyrus ($ps < .01$). rMDD were characterized by cognitive control deficits, associated with decreased amplitudes in the N450 component, specifically when sad - but not happy - stimuli needed to be inhibited ($ps < .05$). ND, on the other hand, demonstrated enhanced N450, localized to the dorsal anterior cingulate cortex (dACC, BA 24'/32', 6 voxels, $p < 0.005$) during response inhibition for sad faces. Moreover, this activation in the dACC was correlated to self reports of suppression as an emotional regulation strategy ($ps < .005$).
Conclusions: These results show that rMDD demonstrate no overall deficits in cognitive control, but that these impairments are specific to emotional stimuli. Compared to ND, rMDD demonstrate a slower response inhibition to sad faces, associated with decreased conflict monitoring processes. The relationship between attentional bias, emotion regulation and vulnerability to depression will be discussed.
Supported by FWO08/PDO/168; F32 MH081394; R01 MH068376, R21 MH078979; R21 AT002974; NARSAD Independent Investigator Award

219. Visual Affect Recognition Accuracy Differences by Psychiatric Illness

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Background: Dysregulation in emotion recognition and processing is gaining recognition as hallmark feature of many psychiatric illnesses and medical conditions with psychiatric features. Deficits in processing affective stimuli may have both neurobiological and performance substrates.
Methods: Individuals were classified with the structured interview and were recruited through several studies at the University of Michigan Health System. Individuals with Major Depressive Disorder (MDD) (n=165), Bipolar Disorder (BD, n=183), MDD with comorbid Anxiety Disorder (n=53), MDD with comorbid history of Dysthymia (n=20), and Cushing's Disorder (CD, n=19), were compared to healthy controls (n=176) on a task of affect identification via facial stimuli (FEPT). Participants were asked to identify which of the four emotions (happy, sad, angry, fear) was displayed.
Results: Significant group differences were found on overall FEPT accuracy rate. Post hoc analyses revealed that compared to healthy controls individuals with MDD, BD, and CD had significantly more difficulty identifying emotional facial stimuli ($p<.01$). HC were also significantly stronger in identifying fear compared to MDD, MDD with comorbid anxiety, and BD ($p<.05$). MDD, BD, and CD demonstrated difficulty with identification of sad stimuli compared to HC ($p<.05$). BP and CD subjects had difficulty identifying happy stimuli compared to MDD with comorbid dysthymia ($p<.05$). BD also had difficulty identifying happy stimuli compared to HC ($p<.05$). All groups except BD performed better than CD identifying angry stimuli ($p<.05$).
Conclusions: A number of contrasts were found for accuracy in emotional categories between psychiatric diagnoses. Future analyses will look at specific emotion biases analyses.
Supported by Prechter Longitudinal Bipolar Project, t he Rachel UpJohn Clinical Scholars Award, NIH grant P01MH 42251, internal support from the Depression and Neuropsychology Divisions of the Department of Psychiatry of the University of Michigan

220. Biochemical Changes in Neurotensin Receptor Null Mice: Relevance to Schizophrenia

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Background: Neurotensin is a neuromodulator that acts mainly through two neurotensin receptors, NTS1 and NTS2. Neurotensin modulates the dopaminergic and glutamatergic systems implicated in the pathogenesis of schizophrenia. Using mice lacking either NTS1 ($NTS1^{-/-}$) or NTS2 ($NTS2^{-/-}$), the effects of NT receptors on the dopaminergic and glutamatergic function were determined.
Methods: *In vivo* microdialysis in freely moving mice, coupled with HPLC-ECD, was used to detect basal and *d*-amphetamine-stimulated striatal extracellular dopamine levels. Striatal D-serine and PFC glutamate levels were determined by capillary electrophoresis. *In vitro* radioligand binding and synaptosomal uptake assays for the dopamine transporters (DAT) were conducted to test for the expression and function of the striatal pre-synaptic DAT. Dopamine D2 (DAD2) expression was determined in the ventral tegmental area (VTA).
Results: $NTS1^{-/-}$ and $NTS2^{-/-}$ mice had higher basal extracellular dopamine levels in striatum. $NTS1^{-/-}$ mice showed exaggerated dopamine release in response to *d*-amphetamine. Both $NTS1^{-/-}$ and $NTS2^{-/-}$ mice exhibited lower DAD_2 receptor mRNA expression in the VTA relative to wild-type mice. DAT binding and dopamine reuptake in striatum were not altered. Additionally, $NTS1^{-/-}$ exhibited significantly lower striatal D-serine and PFC glutamate levels as compared to wild- type mice.
Conclusions: The lack of NTS1 or NTS2 alters the dopaminergic and glutamatergic systems. A deficiency in glutamate neurotransmission may cause the dysregulation of the dopamine system. These data strengthen the hypothesis that NT receptors are involved in the pathogenesis of schizophrenia through modulating the dopaminergic and glutamatergic systems and provide a potential model for the biochemical changes of the disease.
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221. Differential Protein Expression of Risperidone and Paliperidone in Rat Pre-Frontal Cortex: A Dose Response Comparison

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Background: Risperidone is an atypical antipsychotic used to treat schizophrenia. Its major active metabolite 9-hydroxy-risperidone has similar pharmacodynamics although it is not extensively metabolized in the liver. While their specific mechanism of action is unknown, it is thought that paliperidone and risperidone act via similar, if not identical, pathways. We report differences in synaptoneurosomal protein expression in the rat pre-frontal cortex after chronic treatment with paliperidone compared to risperidone.
Methods: Synaptoneurosomal preparations from risperidone and paliperidone treated rats (28 daily i.p injections) were isolated from pre-frontal cortex (PFC). 2D-DIGE and mass spectrometry were used to separate and identify differentially expressed proteins. Differences in spot intensity were determined using risperidone/paliperidone intensity ratios for 0.2, 0.5, and 1.0 vs 2.0 mg/kg doses, respectively.
Results: Our results indicate that chronic treatment with risperidone and paliperidone at different dosages induced different responses in protein expression in synaptoneurosomal preparations from rat prefrontal cortex. While some proteins were up-regulated in the paliperidone- treated group by two fold or greater compared to the risperidone treated group, others remained unchanged and some were down-regulated by two fold or more. Proteins were also differentially expressed depending on the dose used.
Conclusions: Our results suggest that chronic risperidone and paliperidone treatment results in differential expression of rat PFC synaptoneurosomal proteins in a dose-dependent manner indicating possible differences in the mechanism of action of these two drugs at the synaptoneurosomal level.
Supported by Ortho-McNeil Janssen Scientific Affairs, L.L.C

222. Glutamate-Dopamine Interactions in a Maternal Immune Activation Model with Relevance to Schizophrenia

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Background: Maternal immune activation is a suspected risk factor for schizophrenia. Rodents exposed to maternal immune activation develop behavioral, neurochemical, and neuroanatomical abnormalities relevant to positive and cognitive symptoms of schizophrenia. Dysregulation of glutamate-dopamine interactions has been hypothesized to underlie schizophrenia pathogenesis, as well as the behavioral abnormalities observed in animals exposed to maternal immune activation. In the present study, we investigated dopamine D3 and NMDA receptor interactions after maternal immune activation.
Methods: Pregnant Sprague Dawley rats were injected with polyinosinic:polycytidylic acid (poly I:C) or vehicle on gestational day 14. The effects of the highly selective dopamine D3 receptor antagonist NGB 2904 on the locomotor response to NMDA receptor antagonist MK-801 were determined in male offspring of poly I:C and vehicle treated dams on postnatal day 56.
Results: Pretreatment with NGB 2904 enhanced the locomotor response to MK-801 in offspring of vehicle treated dams, but attenuated MK-801-stimulated locomotion in offspring of poly I:C treated dams.
Conclusions: Dopamine D3 receptor antagonism has *opposing* effects on the locomotor-activating action of NMDA receptor antagonism in offspring of poly I:C and vehicle treated dams. D3 antagonism enhances MK-801-induced locomotion in control offspring, but attenuates this response after maternal immune activation. These data suggest the D3 receptor modulates the response to NMDA receptor antagonism. Further, these data identify alterations in dopamine D3-glutamate interactions after maternal immune activation, and provide evidence for underlying decreased D3 receptor activity. In combination, these data suggest loss of D3 receptor inhibition may contribute to behavioral changes following maternal immune activation.
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223. Metabolic Alterations in the Cortex of a Mouse Model with Glutathione Deficit - Relevance to Schizophrenia

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Background: Glutathione (GSH) is reduced in cerebrospinal fluid and prefrontal cortex of schizophrenia patients. Key GSH-synthesizing enzyme genes, glutamate-cysteine ligase catalytic (GCLC) and modifier (GCLM) subunits, are associated with schizophrenia, suggesting a genetic origin for impaired GSH synthesis. This redox deregulation associated to environmental oxidative stress may have a central role in schizophrenia. GCLM knock-out (KO) mice, which display reduced brain [GSH] and abnormal brain morphology and function, were used to investigate the impact of a genetically dysregulated redox system on the neurochemical profile of the developing cortex.
Methods: The neurochemical profile (18 metabolites) was determined by *in vivo* 14.1T proton-NMR spectroscopy in anterior and posterior cortex.
Results: GCLM-KO mice displayed nearly undetectable GSH levels as compared to WT mice. GSH depletion triggered alteration of its metabolic precursors, namely increase of glycine and glutamate levels during development (P20-P30). Glutamine and aspartate, produced from glutamate, were also increased in GCLM-KO animals. In addition, GCLM-KO mice showed higher *N*-acetylaspartate concentration that originated by aspartate acetylation. These metabolites are implicated in neurotransmission and mitochondrial metabolism. Their increase may indicate impaired mitochondrial function with concomitant accumulation of lactate in adult mice (P60-P90). Furthermore, GSH depletion induced reduction of GABA concentration in anterior cortex of the P60 mice, reflecting the known impairment of GABAergic interneurons in that area.
Conclusions: The observed metabolic alterations in the cortex of a mouse model of redox dysregulation suggest impaired mitochondrial metabolism and altered neurotransmission and highlight P20-P30 as a sensitive period during the development for these alterations.
Supported by Swiss National Science Foundation, Loterie Romande

224. Human Endogenous Retrovirus in Schizophrenia: A New Avenue of Research at the Gene-Environment Interface

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Background: Schizophrenia is a complex disease with genetic background interacting with environmental factors. In this respect, identification of such environmental factors and their interplaying genes is critical for developing innovative therapeutic approaches.
Methods: Epidemiological data, post-mortem as well as brain imaging studies have shown that schizophrenia is likely to begin with neurodevelopment impairment occurring early in life.
Independent molecular studies have shown an association between Human Endogenous Retroviruses type "W" family (HERV-W) and Schizophrenia, mostly by PCR studies, but none had yet addressed specific antigen detection in living patients. We have thus recently performed an exploratory study, in which HERV-W GAG and ENV proteins were quantified in the serum with a dedicated immunoassay among 50 schizophrenic patients (*versus* controls).
Results: In schizophrenic patients, positive antigenaemia for both ENV and GAG antigens was found in nearly half of the patients ($p<0,01$ for ENV; $p<0,001$ for GAG). Moreover, a significant correlation between ENV antigenaemia (a protein causing dysimmune inflammatory effects) and C-Reactive Protein levels (CRP, a systemic inflammation biomarker), was found in patients known to evolve towards cognitive decline with neuronal loss.
Conclusions: This now opens perspectives for an hypothesis related to the pathogenic impact on schizophrenia of a yet poorly known category of biological elements, i.e. Human Endogenous retroviruses (HERVs). As part of the genetic mobile (transposable and retrotransposable) elements representing 42% of the human genome, they have probably played a "beneficial" role in the genome modifications underlying the evolution of species yielding adapted responses to environmental influence.

225. Assessing Mechanisms of Reduced Cannabinoid 1 Receptor (CB1R) Expression in Schizophrenia: Contribution of Reduced GAD67 mRNA Expression

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Background: Lower CB1R mRNA and protein levels are common and conserved across dorsolateral prefrontal cortex (DLPFC) regions in schizophrenia. Furthermore, changes in CB1R mRNA expression in schizophrenia significantly correlate with those of GAD67, a synthesizing enzyme for GABA, suggesting that CB1R-containing neurons exhibit deficient GABA synthesis. Because activation of CB1Rs suppresses the release of GABA, lower CB1R levels could be a compensatory response to reduce endocannabinoid-mediated suppression of GABA release in subjects with schizophrenia.
Methods: Using quantitative in situ hybridization, we measured CB1R and GAD67 mRNA levels in the medial prefrontal cortex of genetically engineered GAD67 heterozygous (GAD67+/-), CB1R heterozygous (CB1R+/-), CB1R knockout (CB1R-/-) and matched wild-type mice.
Results: In GAD67+/- mice, GAD67 and CB1R mRNA levels were significantly reduced by 37% and 15%, respectively, relative to wild-type mice. CB1R and GAD67 mRNA levels correlated across animals ($r=0.61$; $p=0.01$), suggesting that CB1R mRNA levels parallel those of GAD67 mRNA. In CB1R+/- and CB1R-/- mice, CB1R mRNA levels were significantly lower by 50% in CB1R+/- mice and completely absent in CB1R-/- mice. GAD67 mRNA levels were unaltered in CB1R+/- and CB1R-/- mice.
Conclusions: These findings demonstrate that reduced GAD67 mRNA expression is sufficient to produce reduced CB1R mRNA expression and suggest that lower CB1R mRNA expression in the DLPFC of subjects with schizophrenia may be driven by lower GAD67 mRNA expression. These observations support the hypothesis that lower cortical levels of CB1Rs levels in schizophrenia may partially compensate for deficient GAD67-mediated GABA synthesis by reducing endogenous cannabinoid suppression of GABA release.
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226. Adult-Onset Glutamate Receptor Expression Deficits in the Hippocampus of Glutaminase-Deficient Mice

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Background: Glutaminase-deficient mice (GLS1 hets), with reduced glutamate recycling, have a focal reduction in hippocampal activity and a selective deficit in hippocampal-dependent contextual learning. We asked whether expression of other enzymes in the glutamate-glutamine recycling pathway or glutamate receptors was affected in the hippocampus of GLS1 hets.
Methods: We collected hippocampal and cortical samples from GLS1 het and littermate controls at 3 ages and assessed gene expression using Affymetrix gene chips and rtPCR. We compared GLS1 hets to NR1 hypomorphs, which model aspects of schizophrenia. Additionally, we examined context-dependent fear conditioning.
Results: In adult mice, GLS1 was downregulated, as expected, by ~50%, while enzymes in related metabolic pathways were unaffected. Misexpression was prevalent in long-term plasticity pathway genes. GluR2 was downregulated by ~40%. rtPCR confirmed the latter finding and further revealed an increase in GluR2 in cortex. GluR2 and NR1 expression were unaffected in adolescence. Gene expression in GLS1 hets differed significantly from NR1 hypomorphs. Contextual fear conditioning was unaffected in adolescence, but disrupted in adulthood, as we had shown previously.
Conclusions: GLS1 deficiency does not affect other metabolic pathways, but does lead to adult-onset alterations in glutamate receptor levels, possibly accounting for adult onset alterations in context-dependent learning. In the context of current knowledge on glutamate abnormalities in schizophrenia, and since GLS1 het gene expression patterns differ striking from NR1 hypomorphs, these findings support the idea that GLS1 hets do not model schizophrenia, and that inhibition of glutaminase in adulthood may in fact prove therapeutic in this disorder.
Supported by T32 DA016224 (IGS), P50 MH066171 (SR), K02 DA000356 (SR)

227. Attenuation of Phencyclidine (pcp)-Induced Novel Object Recognition (nor) Deficit by the Combination of the Atypical Antipsychotic Drugs (apd), Clozapine or Lurasidone, with Metabotropic Glutamate Receptor (mglur) 2/3 Agonist, Ly379268.

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Background: NOR in rodents is a parahippocampal-based cognitive function which is considered relevant to human long term declarative memory. Sub-chronic treatment with the NMDA receptor non-competitive antagonist, PCP, produces a NOR deficit which is partially attenuated by atypical APDs, including clozapine(CLO) and lurasidone(LUR), a serotonin-dopamine antagonist, but not by typical APDs, e.g. haloperidol(HAL, Grayson et al., 2007; Snigdha et al., in press). We tested the hypothesis that the mGluR2/3 agonist, LY379268, would potentiate sub-effective dose of LUR or CLO, but not HAL or the 5-HT_{2A} inverse agonist, pimavanserin(PIM), to reverse the PCP-induced NOR deficit.
Methods: Female Long-Evans rats received vehicle or PCP (2mg/kg) for 7 days, followed by a 7-day washout period (n=6-8/group). On the test day, the rats were treated with sub-effective doses of LUR (0.1mg/kg), CLO (0.1mg/kg), HAL (0.1mg/kg), or PIM (3mg/kg) with or without pretreatment with LY379268 (1mg/kg), prior to NOR testing.
Results: Vehicle-, but not PCP-treated, rats, explored the novel object significantly more than the familiar in the retention trial. LY379268 alone did not attenuate the PCP-induced deficits in NOR. However, co-administration of LY379268 with sub-effective doses of LUR or CLO, but not HAL or PIM, significantly reversed the PCP-induced deficits.
Conclusions: These results indicate that mGluR2/3 agonism is relevant to the ability of atypical APDs to ameliorate the effect of sub-chronic PCP on NOR. This suggests combined administration of a mGluR2/3 agonist with at least some atypical APDs may be a way to enhance their efficacy for cognition in schizophrenia.
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228. Hippocampal Oscillations in the Rodent Model of Schizophrenia Induced by Amygdale Gaba Receptor Blockade

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Background: Brain oscillations are critical for cognitive processes, and their alterations in schizophrenia are proposed to contribute to cognitive impairments. Network oscillations primarily rely upon GABAergic interneurons, which also show characteristic changes in schizophrenia. The aim of this study was to examine the capability of hippocampal networks to generate oscillations in a rat modal of schizophrenia exhibiting schizophrenia-relevant alterations in hippocampal GABAergic circuits (Beretta at al., 2004), critical to oscillatory network synchronization.
Methods: The model of Berretta and Benes (Nat. Protocols, 2006) were regenerated in adult Sprague-Dawley rats and studied in three different experiments over the course of this study. This model uses injection of picrotoxin, a non-competitive GABA-A receptor antagonist, into the baso-lateral amygdala (BLA), which strongly projects to the hippocampus and releases glutamate affecting PV+ interneurons of this region. Changes were measured in spontaneous theta rhythm in anesthetized and freely moving animals, and in theta induced by stimulation of the pontine reticular formation under urethane.
Results: We found subtle alterations in theta parameters. In rats reanesthetized with urethane, the standard assay of the stimulus intensity_theta frequency relationship revealed an impairment of generating high frequency theta rhythm whereas in freely moving rats, significant deficit was only observed in the deep theta dipole during exploration.
Conclusions: The results of this study indicate that the selective excitoxic disruption of interneuron signaling in the hippocampus mediated through an over-activation of the input from the amygdala, as a model of schizophrenia, results in complex alterations in the oscillation patterns in the hippocampus.
Supported by NIMH

229. Effects of Disc1 Truncation and Levodopa Metabolism on Mouse Open Field and Circadian Wheel-Running Behavior

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Background: Schizophrenics display several phenotypic changes, including sleep disturbance, some of which are believed to be associated with aberrant dopamine transmission. We examined circadian and open field behavior (OFB) in mice carrying a truncation in the *Disc1* gene (a risk factor for schizophrenia) with and without chronic Levodopa treatment at younger and older adult ages in order to determine whether *Disc1* truncation and Levodopa treatment alter these behaviors.
Methods: Circadian wheel-running activity was monitored in one cohort of male and female mice at post-natal day 110 (P110) in a 12:12 Light:Dark photoperiod (LD) and in constant dark (DD). At P175 phase response to a light pulse at circadian time 15 hours was measured. LD and DD assays were repeated at P232. A second cohort of mice, all male, was implanted with timed-release Levodopa capsules at P60. Open field behavior was observed at P70 for 7 minutes, followed by circadian rhythm assays and OFB re-testing at P113. Total square entries (TSE) for OFB estimated overall activity, whereas central square entries (CSE) estimated anxiety.
Results: Cohort one demonstrated significant sex differences for most circadian variables, but no *Disc1* effect or *Disc1* by sex interaction. Cohort two showed no treatment effects of *Disc1* and Levodopa for circadian measures or OFB at P70, but at P113 a significant Levodopa by *Disc1* interaction occurred for TSE and CSE. As CSE = TSE - PSE (peripheral square entries), these results indicate that the effect observed in TSE is driven by that in CSE.
Conclusions: These findings suggest that increased dopamine metabolism and *Disc1* truncation do not alter circadian behavior, but may affect adult neuroplasticity in a manner that alters anxiety behavior only in older stages of adulthood.

230. Involvement of Neurotensin Receptor Subtype 1 in the Neuronal Mechanisms of Acute and Chronic Phencyclidine-Induced Schizophrenia-Like Signs: Behavioral, Neurotransmitter, and Molecular Studies

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Background: Our recent work shows that a NT analog is effective in blocking phencyclidine (PCP)-induced schizophrenia-like signs, which may be partly mediated through NT subtype 1 receptor (NTS1). The present study was conducted to determine the effect of NTS1 deletion on acute and chronic PCP-induced schizophrenia-like signs with the use of NTS1 knock-out ($NTS1^{-/-}$) mice.
Methods: Basal, acute (5 mg/kg, i.p.), and chronic (21 days 5 mg/kg i.p.) PCP-induced locomotor activity and immobility were determined. *In vivo* microdialysis was used to detect basal, acute, and chronic PCP-stimulated extracellular DA and amino acid levels in medial prefrontal cortex (mPFC). Total mRNA expressions of DA and NMDA receptors in mPFC were determined by real-time PCR analyses.
Results: $NTS1^{-/-}$ had significantly higher immobility and lower PCP-induced hyperactivity than did WT mice. Chronic PCP (CP) administration trended toward a reduction of locomotor activity and enhancement of immobility in WT mice. $NTS1^{-/-}$ and CP-WT mice showed similarly lower basal glutamate levels and acute PCP-induced DA and glutamate release in mPFC. Moreover, both $NTS1^{-/-}$ and CP-WT mice had lower mRNA expression for DAR1, DAR2, and NMDAR2A receptors in mPFC. DAR1 was up-regulated in CP-$NTS1^{-/-}$ mice.
Conclusions: $NTS1^{-/-}$ mice showed similarities to WT mice chronically treated with PCP in regard to schizophrenia-like behavior, as well as the neurochemical and molecular changes in mPFC. Additionally, a possible novel interaction of $NTS1/DAR_1$ receptors in mPFC may be involved in the schizophrenia-like behavioral changes. (This work was funded by NIH grant MH71241.)
Supported by MH71241

231. Vesicular Monoamine Transporter 1 (VMAT1) Knock-Out Mice Display a Hyper-Dopaminergic Phenotype - Implications for Psychotic Disorders

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Background: Genetic variation in the human vesicular monoamine transporter 1 (VMAT1) gene on chromosome 8p have been associated with increased risk for bipolar disorder and schizophrenia. Given recent evidence of VMAT1 brain expression and its biological role in presynaptic monoaminergic neurotransmission, we used a knock-out mouse model to investigate biochemical and behavioral consequences of VMAT1/slc18a1 deficiency.
Methods: VMAT1 null-mutant mice were generated using gene targeting. Mice were raised as littermates by heterozygote breeding on a C57BL/6 genetic background. Wildtype (+/+), heterozygote (+/-) and null-mutant (-/-) mice were examined at 8-12 weeks of age for mRNA and protein expression, monoaminergic tissue content, and were behaviorally assessed for baseline locomotor activity, antidepressant effects using the tail-suspension test (TST), and for amphetamine sensitivity using an amphetamine challenge locomotor test.
Results: VMAT1 null-mutant mice are viable and display a hyper-dopaminergic phenotype. Dopamine levels were significantly increased in frontal cortex and striatum in -/- mice compared to +/+. The TST revealed an antidepressant effect for -/- animals. Amphetamine challenge revealed a significant increase in locomotor activity for -/- mice compared to +/+.
Conclusions: VMAT1 null-mutant mice display high dopamine levels in key brain structures involved in several neuropsychiatric disorders and display behavioral phenotypes relevant to monoaminergic neurotransmission. Given the fundamental role of dopamine in the pathophysiology of psychotic disorders such as schizophrenia and bipolar disorder, this mouse model might be useful in the investigation of presynaptic neurotransmission and VMAT1 involvement in neuropsychiatric disorders.
Supported by K08MH080372

232. Effects of Pramipexole on Sensorimotor Gating and cAMP/PKA Signaling in the Nucleus Accumbens

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Background: The dopamine D3 receptor (D3R) is being examined as a target for novel neuropsychiatric pharmacotherapies. Compared to D2R, relatively little is known about the *in vivo* intracellular signaling cascade of the less-abundant D3R. We previously reported that, at doses that disrupt prepulse inhibition (PPI), the mixed D1/D2-like receptor agonist apomorphine and the preferential D3 agonist pramipexole decreased c-fos expression in rat nucleus accumbens (NAC), a region known to be involved in the dopaminergic

regulation of PPI. In this study, we measured cAMP levels, protein kinase A (PKA) activity, and CREB phosphorylation (a transcription factor for c-fos) in the NAC after administration of apomorphine or pramipexole.
Methods: Adult, male Sprague-Dawley rats were administered apomorphine (0, 0.25 mg/kg) or pramipexole (0, 0.3, 1.0 mg/kg) subcutaneously prior to either brain tissue removal or perfusion with para-formaldehyde. cAMP levels or PKA activity were analyzed via ELISA. Perfused brain tissue was reacted with antibodies for CREB and phosphorylated CREB before quantification of immunostained profiles
Results: At doses known to disrupt PPI and reduce c-fos expression, both apomorphine and pramipexole decreased PKA activity and CREB phosphorylation in the NAC. Studies testing the effects of apomorphine and pramipexole effects on cAMP in the NAC are under way.
Conclusions: We show that both non-selective and D3-selective dopamine agonists alter the cAMP/PKA signaling cascade, which likely contributes to decreases in CREB phosphorylation. Effects described here may represent a non-divergent signaling pathway for D2 and D3 receptor activation.
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233. Pramipexole Infusion into the Nucleus Accumbens Disrupts Prepulse Inhibition in Rats

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Background: Previous studies have shown that systemic administration of dopamine D3-preferential agonists like pramipexole disrupts prepulse inhibition of startle (PPI) in rats. Given the high density of D3 receptors in the nucleus accumbens (NAC), and the prominent role of this brain region in mediating dopamine agonist-induced PPI deficits, we hypothesized that the NAC may also play a critical role in mediating pramipexole-induced PPI deficits. Here we tested this hypothesis by infusing pramipexole directly into the NAC.
Methods: Pramipexole (0, 3, 10 µg/0.5µl/site) was infused bilaterally into the NAC of male Sprague Dawley rats prior to PPI testing.
Results: Pramipexole significantly decreased PPI, while startle responses were not significantly affected.
Conclusions: The present findings demonstrate that infusion of the preferential D3 agonist pramipexole into the NAC is sufficient to disrupt PPI in rats. These studies highlight the role of D3 (and potentially D2) receptors in the NAC in mediating dopamine agonist-induced PPI deficits. Experiments in progress are assessing the anatomical specificity of this pramipexole effect in regions with low levels of D3 receptors.
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234. The Effects of the Dopamine D2 Agonist Sumanirole on Prepulse Inhibition in Rats

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Background: Non-selective dopaminergic agonists are widely used to induce prepulse inhibition (PPI) deficits in predictive rat models for schizophrenia. The role of dopamine receptor subtypes in inducing these deficits, however, has remained elusive. In particular, it has been difficult to parse effects linked to D2- vs. D3-receptor activation.
Methods: Here, we characterized the effects of sumanirole (0, 0.3, 1.0, 3.0 mg/kg), a novel selective D2 agonist, in a battery of PPI assays in male Sprague Dawley rats.
Results: All active doses of sumanirole decreased PPI using stimulus parameters widely used in standard PPI sessions. The effects of sumanirole (0, 3 mg/kg) were completely opposed by very low doses of the D2-preferential antagonist L741626 (0, 0.3, 0.6 mg/kg) supporting a D2-receptor linked mechanism of action. Using a PPI session with various prepulse intervals, sumanirole decreased PPI at 60-120 ms prepulse intervals, and increased PPI at 10-20 ms intervals.
Conclusions: The present findings demonstrate that D2 receptor activation is sufficient to disrupt PPI deficits in rats, even at sumanirole doses that would be predicted to have no appreciable co-activation of either D1 and/or D3 receptors. Such a selective D2-receptor linked mechanism of action of sumanirole on PPI will be valuable in parsing the neurobiological basis of antipsychotic-like effects in rodent PPI models. In particular, sumanirole may be valuable in interpreting findings in *in vivo* assays that use PPI to detect D3-preferential antagonists.
Supported by R01 MH068366

235. Elevated SHMT1 Level Leads to Lowed Glycine Availability and Reduced Prepulse Inhibition in Mice and is Associated with Schizophrenia: A New Molecule Relevant to NMDA Theory of Schizophrenia

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Background: Deficits in prepulse inhibition (PPI) are thought to be a biological trait of mental illnesses, including schizophrenia. To identify schizophrenia susceptibility genes, we previously searched for PPI-controlling genomic elements, by performing quantitative trait loci (QTL) analysis in mice derived from crossing C57BL/6 (B6) mice showing high PPI with C3H/He (C3) mice displaying low PPI. The detected QTLs included one on chromosome 11, which decreases PPI in C3 genomic substrate(s). In this study, we have focused on this QTL.
Methods: Two candidates in the 95% confidence interval of the lod peak are mapped: the genes for serine racemase (Srr) and serine hydroxymethyltransferase 1 (Shmt1). Both genes encode enzymes in the cascade of syntheses of D-serine and glycine, which are endogenous co-agonists for the N-methyl-D-aspartate type glutamate (NMDA) receptor. Dysfunction of NMDA receptor in impaired PPI and schizophrenia is well known.
Results: Our biochemical analyses revealed that the availability of D-serine and glycine as neuromodulators in the frontal cortex is higher in B6 than in C3 mice, corresponding to a better PPI performance in B6 mice. The transcript expression data for B6 and C3 mice and also in human schizophrenia postmortem brains points to Shmt1 as a causative gene. Luciferase analysis unveiled distinctive promoter activity between B6 and C3 genomes.
Conclusions: These results strongly suggest that the different promoter sequences found in Shmt1 could explain at least one of the chromosome 11 PPI-QTL substrates and warrant further investigation into the role of SHMT1 in schizophrenia.

236. Myelin-Associated Proteins in Prefrontal Grey and White Matter in Schizophrenia and Bipolar Disorder.

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Background: White matter abnormalities, including decreased diffusion anisotropy, have been reported in schizophrenia (SCZ) and bipolar disorder (BPD), although the molecular correlates remain unclear. While previous post-mortem studies have identified diminished levels of myelin-associated proteins in grey matter in SCZ, similar studies in white matter are inconclusive. The aim of this study was to quantify myelin-associated proteins in grey and adjacent white matter in a large series of SCZ and BPD cases. In addition, the effect of antipsychotics on myelin-associated proteins was examined in a rat model.
Methods: Samples of prefrontal grey and white matter, comprising SCZ (n=35), BPD (n=34) and control (n=35) subjects, were acquired from the Stanley Medical Research Institute. Frontal grey and white matter was also obtained from male rats following sub-chronic administration of haloperidol, clozapine or vehicle. Myelin basic protein (MBP) and proteolipid protein levels were quantified by ELISA. Myelin associated glycoprotein (MAG) and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) levels were assessed by immunoblotting. Myelin protein levels were compared between groups by ANOVA.
Results: Lower levels of MBP, CNP and MAG were observed in grey matter in SCZ, while CNP and MAG immunoreactivity was also decreased, to a lesser degree, in white matter in this group. However, these differences failed to reach statistical significance. Myelin protein levels were not altered following sub-chronic antipsychotic administration.
Conclusions: Our data does not support a role for myelin-associated proteins in white matter abnormalities in SCZ and BPD. Neither typical nor atypical antipsychotics had any effect on myelin protein levels.
Supported by Funding was provided by Michael Smith Foundation for Health Research, Stanley Medical Research Institute, Canadian Institutes of Health Research (MOP-14037, NET-54013, MOP-81112).

237. GAD67 Protein Levels in the Dorsolateral Prefrontal Cortex of Subjects with Schizophrenia.

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Background: Impaired GABA neurotransmission in the dorsolateral prefrontal cortex (DLPFC) may contribute to the cognitive deficits of schizophrenia. Reduced expression of the mRNA encoding the 67-kDa, but not the 65-kDa, isoform of glutamic acid decarboxylase (GAD), the enzyme that synthesizes GABA, has been widely-replicated. However, protein levels of GAD isoforms have not been thoroughly examined.
Methods: We assessed by western blot the effect of postmortem interval (PMI) in monkey and human DLPFC. In both species, there was a substantial effect of PMI on GAD65 protein levels, while GAD67 protein was well-preserved. Therefore, we quantified only GAD67 protein levels in 19 pairs of control and schizophrenia subjects, matched completely for sex and as closely as possible for age and PMI. All subjects had a PMI < 20 hrs and an RNA integrity number (RIN) > 7. GAD67 protein levels were measured with a specific antibody, and divided by corresponding levels of a loading control, tubulin, in the same sample.
Results: Total GAD67 protein levels were significantly reduced by 10.1% in the DLPFC of schizophrenia subjects compared to controls, and there was no effect of storage time, sex, diagnosis of schizoaffective disorder, or antipsychotic use at time of death. There was a trend-level significant correlation of the within-pair percent difference in GAD67 mRNA (assessed via qPCR) and protein.
Conclusions: These data are consistent with the hypothesis that a reduction in GAD67 mRNA results in less protein, and suggestive of reduced GABA synthesis and subsequent impaired inhibitory neurotransmission in the DLPFC in schizophrenia.
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238. GABAA alpha1 Subunit mRNA Expression in Pyramidal Cells and Interneurons in the Dorsolateral Prefrontal Cortex of Schizophrenia Subjects

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Background: Gamma oscillations are associated with cognitive processing, are impaired in schizophrenia and depend upon parvalbumin (PV) basket cell activity. PV basket cells robustly innervate the perisomatic region of pyramidal cells via $GABA_A$ receptors containing $alpha_1$ subunits. Our laboratory has recently determined that mean $GABA_A$ $alpha_1$ subunit mRNA expression is 18% lower in the DLPFC of schizophrenia subjects, most prominently in layer deep 3. However, the decrease in $alpha_1$subunit mRNA may not be specific to pyramidal cells as $alpha_1$ subunits are also present in interneurons.
Methods: Dual-label *in situ* hybridization studies were performed to quantify $alpha_1$ subunit mRNA levels in pyramidal cells and interneurons using tissue from 14 matched pairs of schizophrenia and comparison subjects. Specific ^{35}S -labeled riboprobes for $GABA_A$ $alpha_1$, and digoxigenin (DIG)-labeled riboprobes for calcium/calmodulin-dependent kinase IIalpha (CaMKIIalpha) to identify pyramidal cells and GAD_{65} to identify interneurons were designed. The number of $alpha_1$ subunit grains per DIG-labeled neuron was determined in layer deep 3 of area 9.
Results: Analysis was performed with a mean (SD) number of 1,681 (16.9) and 2,061 (31.0) pyramidal cells counted for comparison and schizophrenia subjects, respectively. Mean $alpha_1$ subunit grain density per pyramidal cell was significantly ($p = 0.004$) 40% lower in schizophrenia subjects. Blinded studies are ongoing for interneurons.
Conclusions: $alpha_1$ subunit mRNA is significantly 40% decreased in layer deep 3 pyramidal cell bodies in schizophrenia subjects, twice the overall tissue reduction (18%). Thus, we predict $alpha_1$ subunit grain density will be unchanged in interneurons of schizophrenia patients.
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239. An Inverse Relationship between Cortisol and BDNF Levels in Schizophrenia: Data from Human Postmortem and Animal Studies

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Background: Stress and stress-induced glucocorticoids have been implicated in many neuropsychiatric disorders including schizophrenia. In addition, the neurotrophin, brain derived neurotrophic factor (BDNF) has been shown to play an important role in stress-mediated changes in neuroplasticity, however, the exact relationship between glucocorticoid and BDNF levels in

schizophrenia is unclear.
Methods: We measured the levels of cortisol (a major glucocorticoid hormone in humans) and BDNF in prefrontal cortex and CSF samples of postmortem schizophrenia subjects. We also assessed the levels of cortisol and BDNF in the frontal cortex and serum from an animal model (the offspring of prenatally stressed rats), which demonstrates several behavioral and neuroendocrine abnormalities similar to schizophrenia.
Results: We found a significant increase in cortisol levels in prefrontal cortex and CSF samples from subjects with schizophrenia. The BDNF levels were significantly lower in prefrontal cortex and CSF samples of subjects with schizophrenia (compared to age-matched controls), and a significant negative correlation between BDNF and cortisol in both prefrontal cortex and CSF was observed. Data from animal studies indicated that prenatally stressed offspring have significantly lower serum and prefrontal cortex BDNF levels, whereas serum cortisol levels were significantly higher when compared to control, non-stressed offspring. In addition, olanzapine treatment for 30 days starting at PND60 significantly attenuated prenatal stress-induced increase in cortisol levels in prefrontal cortex, but no change in BDNF levels was observed after olanzapine treatment.
Conclusions: The above human and animal data support the premise that BDNF plays an important role in stress mediated pathophysiology in schizophrenia.

240. Rapid Tranquillisation for Agitated Patients in Emergency Psychiatric Rooms: A Randomised Trial of Olanzapine, Ziprasidone, Haloperidol Plus Promethazine, Haloperidol Plus Midazolam and Haloperidol

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Background: Agitated or violent behavior, mostly as a result of serious mental illness and
substance misuse, constitutes around 10% of the reasons for use of emergency services worldwide. The knowledge about antipsychotics profile in agitation and aggressive behavior is limited and few studies compare several drugs in rapid tranquilization.
Methods: We recruited 150 patients with acute psychosis and agitation who were admitted at the Psychiatric Emergency Room of Santa Casa de São Paulo (Brazil). They were alternatively allocated to 1 of 5 intramuscular therapeutic arms: olanzapine (10mg), ziprasidone (20mg), haloperidol (5mg) plus promethazine (50mg), haloperidol (5mg) plus midazolam (15mg) and haloperidol (5mg) alone. They were evaluated after one hour, two hours, four hours, six hours and twelve hours by Overt Agitation Severity Scale (OASS), Overt Aggressive Scale (OAS) and Ramsay Sedation Scale (RSS).
Results: All medications improve agitation and aggression scores. After twelve hours olanzapine, haloperidol alone, haloperidol plus promethazine demonstrated the lowest scores for OASS ($p<0.001$) and OAS ($p=0.001$). Haloperidol plus midazolam had the highest levels and was related with more additional dosages ($p=0.032$) and excessive sedation ($p=0.002$). There were no differences of extrapyramidal side effects between these medications.
Conclusions: Besides there were few differences between typical and atypical antipsychotics in acute agitation in psychosis, olanzapine and haloperidol alone showed better efficacy for promote rapid tranquilization in the first 12 hours. Haloperidol plus midazolam had the worst results.

241. Differential Impact of Oral and Long-Acting Risperidone Formulations on Brain Myelination of Adult Schizophrenia Patients

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Background: In previous studies we observed increased white matter volume suggestive of increased myelination in schizophrenic patient groups treated with an atypical antipsychotic (risperidone (Ris)) compared to a typical one. Our initial analyses with long-acting formulation Risperdal Consta (RisC) suggest that it produces better treatment adherence and lower relapse rates than oral Ris. We tested the hypothesis that this long-acting formulation may differentially increase myelination in adults with schizophrenia.
Methods: We performed a randomized parallel arm trial comparing treatment with either Ris (N=9) or its long-acting formulation RisC (N=11) in schizophrenia patients who were within two years of their first psychotic episode. After being clinically stabilized on Ris, subjects were randomly assigned to either treatment arm. MRI scans were obtained prior to randomization and at 6-month follow-up and the change in frontal lobe myelinated white matter volume was assessed.
Results: Preliminary data analyses suggest that the group treated with RisC accumulated significantly more myelinated white matter than the group treated with the oral Ris formulation ($p<.05$).
Conclusions: This observation suggests that in adults with schizophrenia the choice of formulation of antipsychotic treatments may have differential impact on later-myelinating frontal lobe circuitry. MRI can be used to dissect subtle differences in brain tissue characteristics in vivo and help clarify the effect of pharmacologic treatments on developmental and pathologic processes.
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242. Differential Effects of Dextro-Amphetamine Administration in Schizophrenia vs. Healthy Control Subjects

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Background: It has been hypothesized that cortical function may have an inverted-U shaped dependence on dopamine (DA) levels. Given that schizophrenia (SZ) is thought to be associated with decreased cortical DA levels, while healthy control subjects (HC) may already have optimal DA levels, administration of pharmacologic agents that increase cortical DA may improve cortical function in SZ subjects while impairing cortical function in HC. To test this putative relationship, we examined the effect of single-dose dextro-amphetamine (d-Amph) on cortical responses in an auditory click-train paradigm.
Methods: 8 HC and 6 SZ subjects participated in a double-blind, cross-over,

placebo (PBO)-controlled study of single-dose d-Amph administration. After medication administration, subjects had EEG measured during auditory click trains presented at 20, 30 and 40 Hz. The spectral power of the steady-state auditory evoked potential (SSAEP) response was determined with wavelet analyses.

Results: For the PBO condition, SZ showed lower gamma (40 Hz) power compared to HC, replicating previous studies. However, SZ showed improvements in gamma power with d-Amph administration compared to placebo, while HC showed less gamma power with d-Amph compared with PBO.

Conclusions: Our results provide preliminary evidence that increasing cortical dopamine may enhance cortical activity in schizophrenia subjects while impairing cortical responses in healthy subjects, consistent with an inverted-U shaped relationship between cortical activation and dopamine levels. Results will be discussed in terms of possible neurophysiologic effects of dopamine and therapeutic relevance for schizophrenia.

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243. The Heterogeneity of Antipsychotic Response in the Treatment of Schizophrenia

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Background: Schizophrenia is a heterogeneous disorder in terms of response to treatment with many studies reporting about 70% early non-response to treatment. Currently available medications for schizophrenia are effective for only about 50% of patients. This study investigated the heterogeneity in treatment response among schizophrenia patients treated with atypical antipsychotics.

Methods: Growth mixture modeling was applied to data from a randomized, double-blind, 12-week study consisting of 628 patients with schizophrenia or schizoaffective disorder treated with risperidone or olanzapine antipsychotic drugs. Subgroups of patients (latent class) homogeneous in symptom progress during treatment and significantly dissimilar from other subgroups were identified.

Results: Four distinct response trajectories based on the PANSS total score over a 12-week time period were identified. Classes 1 and 2 were uniquely distributed with ≥96% ultimate non-responders (UNR: <40% improvement in PANSS total at endpoint) after 12 weeks of treatment. Patients in Class 3 were a mixture of UNR (87%) and ultimate responders (UR: >40% improvement in PANSS total at endpoint, 13%) after 12 weeks of treatment. Class 4 was uniquely represented with 100% early responders (ER: >20% improvement in PANSS total at Week 2) and 66% progressed to UR after 12 weeks of treatment. Baseline factors with potential influence on the membership of patients in the latent classes of response will be presented.

Conclusions: This study identified 4 distinct treatment response patterns in schizophrenia patients treated with atypical antipsychotics. This heterogeneity may represent discrete endophenotypes of response to treatment with different etiologic underpinnings.

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244. Analysis of Gene Variants Associated with Iloperidone Response in Patients with Schizophrenia Who are Treated with Risperidone or Olanzapine

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Background: To examine whether any of the six single nucleotide polymorphisms (SNPs) previously associated with response to iloperidone are also associated with improved response to risperidone or olanzapine.

Methods: Patients with schizophrenia were assessed for response/non-response (≥20%/<20% improvement in Positive and Negative Syndrome Scale [PANSS] Total score) after 2 weeks of treatment with risperidone 2-6 mg/day. Responders continued risperidone treatment; non-responders were randomly assigned to risperidone or olanzapine 10-20 mg/day for an additional 10 weeks. Associations between baseline-to-endpoint change in PANSS scores and the six SNPs were examined in the risperidone (n=145) and olanzapine (n=51) groups. Genotype frequencies and improvement in PANSS Total scores were analyzed for those SNPs significantly associated with response. Predictive characteristics were calculated.

Results: SNPs *XKR4* rs9643483 and *GRIA4* rs2513265 were significantly associated with response to risperidone ($p<.05$). Directions of effect with specific genotypes were similar to those reported for iloperidone in risperidone- but not olanzapine-treated patients. The impact of specific genotypes on improvement was more pronounced in African American versus White patients. Predictive characteristics observed for response to risperidone were similar to those seen for response to iloperidone.

Conclusions: Of the six SNPs under review, two may signal overall responsiveness to atypical antipsychotic therapy versus specific sensitivity to iloperidone. Future genetic models of responsiveness may explore how race impacts genotype frequencies, and the strength of associations between SNPs and response to medication.

Supported by Lilly USA, LLC, a subsidiary of Eli Lilly and Company

245. Efficacy and Safety of Long-Acting Injectable Paliperidone Palmitate Relative to Long-Acting Haloperidol, Bromperidol and Fluphenazine Decanoate for Long-Term Treatment in Patients with Schizophrenia Using Number Needed to Treat and Number Needed to Harm

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Background: Atypical antipsychotic long-acting injectables (LAIs) such as paliperidone palmitate (PP) are believed to provide a favorable safety profile compared to typical LAIs. Since no trials compared PP directly with typical LAIs, we assessed the relative benefit-risk of PP to typical LAIs using published placebo-controlled trials.

Methods: A computerized search in MEDLINE was conducted. Number needed to treat (NNT), number needed to harm (NNH), and the likelihood of being helped or harmed (LHH) were calculated from published placebo-controlled studies of PP and the following decanoate LAIs: haloperidol (HD), bromperidol (BD) and fluphenazine (FD). NNTs were calculated for psychotic relapse. NNHs were calculated for extrapyramidal symptoms (EPS): akathisia, tremor, and tardive dyskinesia reported as an adverse event, anticholinergic use, and positive Abnormal Involuntary Movement (AIMS) total score.
Results: NNTs for relapse were similar for all LAIs: 2-5. NNHs varied considerably: akathisia 205 (PP) vs. 10 (BD); tremor 69 (PP) vs. -5 (BD); anticholinergic use 30 (PP) vs. 5 (FD); AIMS positive score -33 (PP) vs. 13 (FD). For tardive dyskinesia the NNH was infinity in PP vs. 7 for FD. LHH for preventing relapse vs. anticholinergic use was 15 for PP and 2.5 for FD.
Conclusions: Effect size as measured by NNT for relapse was similar across different LAIs. NNHs for EPS and related events were lower for typical LAIs as compared to PP. Although the benefits in prevention of relapse are similar among LAIs, the risks of EPS vary considerably. PP has a favorable LHH as compared to typical LAIs.
Supported by Johnson & Johnson Pharmaceutical Research & Development, LLC

246. The Power of Sham rTMS on Chronic Hallucinated Voices in Schizophrenia Patients: An fMRI-Guided rTMS Randomized, Double-Blind, Sham-Controlled Study

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Background: Hallucinations have been associated with changes in superior temporal gyrus (STG) activations. Repetitive transcranial magnetic stimulation (rTMS) over temporal regions has been proposed as a treatment for resistant hallucinated voices in schizophrenic patients, but so far, results in this research field have been inconclusive. We aimed at testing low frequency rTMS over language-related posterior temporal area in patients with chronic schizophrenia and hallucinated voices resistant to at least two antipsychotics.
Methods: Twenty-eight patients were included in a randomized, double-blind, sham-controlled trial using 1-Hz repetitive TMS at 100% motor threshold intensity, over ten 20-min sessions. Stimulation was performed over the STG, at a location defined using fMRI and a language recognition task, in the dominant hemisphere, to create a target for rTMS. Sham stimulation was performed using a sham coil.
Results: Fifteen patients were randomized to active rTMS, and 13 to sham rTMS. Hallucinations severity was assessed at baseline and after 10 rTMS sessions, using the SAPS. Active and sham rTMS similarly decreased the SAPS hallucinations score by 35-40%, but no difference was found between both treatment modalities.
Conclusions: A marked placebo effect of rTMS was observed in this group of resistant schizophrenic patients with hallucinated voices. Active magnetic stimulation of STG regions determined using a language perception task was not better than sham stimulation.
Supported by INSERM_RBM_01-27

247. A Randomized, Double-Blind, Study of Flexible Doses of Paliperidone Palmitate and Risperidone Long-Acting Therapy in Patients with Schizophrenia

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Background: Paliperidone palmitate (PP) is a once-monthly injectable atypical antipsychotic recently approved in the United States for the acute and maintenance treatment of schizophrenia in adults. This study's primary objective was to demonstrate that PP was noninferior to risperidone long-acting injectable (RIS-LAI).
Methods: In this 13-week double-blind (DB) study, consenting adults with schizophrenia (N=1220) were randomized (1:1) to either a) PP: deltoid injections on day 1 (150 mg eq.), day 8 (100 mg eq.), and once-monthly flexible dosing (50-150 mg eq.; deltoid or gluteal) or b) RIS-LAI: gluteal injections on days 8 and 22 (25 mg), days 36, 50 (25 or 37.5 mg), and days 64, 78 (25, 37.5 or 50 mg). RIS-LAI-treated patients received oral supplementation (RIS 1-6 mg/day; days 1-28), and PP-treated patients received oral placebo.
Results: For the per-protocol analysis set (n=765), mean [SD] change from baseline in PANSS total score improved similarly in the 2 groups from day 4 onwards, and at DB endpoint (primary measure) was: PP group, -18.6 [15.45]; RIS-LAI group, -17.9 [14.24]. PP treatment was noninferior to RIS-LAI (point estimate [95% CI]: 0.4 [-1.62;2.38]). The tolerability and safety of PP was similar to RIS-LAI.
Conclusions: PP, with no oral supplementation, was noninferior to RIS-LAI plus oral RIS treatment in patients with schizophrenia. Similar results on the primary efficacy measure between the 2 treatment groups were seen from day 4 onward with the approved initiation regimen of PP used in this study. PP was generally tolerable at the doses tested.
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248. Verbal Working Memory in Cognitive and Symptom Subtypes of Schizophrenia

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Background: Studies using a tone screening test to classify patients have found evidence for schizophrenia subtypes having either verbal working memory (WM) or generalized cognitive deficits. Given the importance of defining

schizophrenia subtypes having distinct cognitive and pathophysiological abnormalities, this study aimed to replicate these findings in larger samples, define symptom features of subtypes, and examine medication effects.
Methods: Patients with schizophrenia who passed the screening test (discriminators, Dsz, n=60) were compared to those who did not (nondiscriminators, NDsz, n=23), and healthy controls (n=52) on a verbal WM test (word serial position test, WSPT) and other neurocognitive tests.
Results: Performance on the WSPT and tone screening test did not differ between medicated and unmedicated patients. Patients who performed as well as controls on the tone screening test (i.e., Dsz) showed poorer performance on the WSPT and a deficit in verbal but not visual memory on the Wechsler Memory Scale-Revised. In contrast, NDsz patients showed overall poor performance on both verbal and nonverbal tests, consistent with a generalized deficit. Verbal WM deficits in Dsz patients were significantly correlated with auditory hallucinations and positive thought disorder ratings, but not with negative symptoms of schizophrenia. As predicted, Dsz patients having auditory hallucinations showed poorer verbal WM than nonhallucinators and controls.
Conclusions: These findings are consistent with neuroimaging findings suggesting that verbal WM deficits in Dsz patients stem from dysfunction of language-related regions in left inferior frontal and temporal cortex, and confirm the value of the tone screening test for parsing schizophrenia into cognitive subtypes.
Supported by RO1MH066597

249. Associative Inference is Impaired in Schizophrenia

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Background: The ability to store the relationship of items in memory relies on the integrity of the hippocampus. Previous studies have shown impairment of relational memory and hippocampal function in schizophrenia. We studied schizophrenia patients with a relational memory paradigm, which tested the ability to identify the novel pairing of stimuli, based on associations learned during training.
Methods: 30 schizophrenia patients and 30 matched healthy control subjects were trained on three sets of paired associates: 30 Face-House pairs (F1-H), 30 Face-House pairs (H-F2, same house with new face), and 30 Face-Face pairs (F3-F4). After training, participants were tested on the previously learned 3 pair types, and on 30 new Face-Face pairs (F1-F2), for which the relationship could only be inferred through associations with the same House.
Results: Schizophrenia patients were less accurate overall (main effect of group, $F=18.04$, $p<.001$). Subjects were more accurate in indentifying the novel (F1-F2) pairs than the previously seen (F3-F4) pairs (main effect of condition, $F=6.27$, $p=.02$). Schizophrenia subjects showed a selective deficit in the associative inference (F1-F2) condition (group by condition interaction, $F=6.27$,$p=.02$). Relational memory performance did not correlate with hippocampal volume ($r=.25$, $p=.21$) and the groups did not differ in hippocampal volume (main effect of group, $F=1.9$, $p=.17$).
Conclusions: We found deficits of relational memory using an associative inference task in a group of patients with normal hippocampal volume. This extends previous studies of relational memory dysfunction in schizophrenia and suggests further studies of the neural substrate of memory function in schizophrenia.
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250. Adolescent-Onset Psychosis and Disrupted Neurocognitive Development: A Cross-Sectional Study of Neuropsychological Performance

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Background: Adolescence is a period of rapid neurocognitive development, especially with respect to the neural circuits linking the prefrontal cortex with other, earlier-maturing brain areas. During this sensitive period, the immature neural assemblies supporting complex, frontally-mediated cognitive functions may be vulnerable to deflection away from their developmental trajectories by the dysplastic processes associated with the onset of psychosis. What remains inadequately characterized is the precise impact of an initial psychotic episode on neurocognitive development, and whether that impact is dependent on age of onset (even within the relatively narrow age range spanning adolescence).
Methods: The present, cross-sectional study involves a comprehensive neuropsychological examination of adolescents experiencing a first-episode of a DSM-IV psychotic disorder (schizophrenia, schizoaffective disorder, and psychosis NOS) and a set of age- and IQ-matched controls.
Results: Although the adolescent-onset psychosis patients displayed a wide range of impairments in domains including short- and long-term memory and executive functioning, areas of greatest disparity between the groups involved fine motor speed and coordination, semantic fluency, and information processing speed. A second set of analyses showed strong associations between age and performance on several measures of short-term memory span and cognitive processing speed, suggestive of relatively late developmental processes constraining behavioral performance efficiency.
Conclusions: These findings suggest that the onset of psychosis during adolescence impedes the optimization of neural assemblies linking prefrontal and posterior cortical regions, resulting in adolescent-onset psychosis patients showing a dramatic loss of neurocognitive efficiency when compared to normally developing controls.
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251. Functional MRI and Dynamic Causal Modeling Reveal Inefficient and Imbalanced Network Interactions in Developmentally Vulnerable Adolescents

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Background: Our purpose was to assess whether brains of schizophrenic offspring differ from those of healthy controls with the use of fMRI and DCM. We want to determine task modulation of intrinsic connections in schizophrenia offspring compared to healthy controls to gain insight into developmental vulnerabilities of schizophrenia. Research in this field is primitive and minimal.
Methods: HC (n=23; age range: 10-19 years) and SCZ_{off} (n=19; age range 8-19 years) participated. Gradient echo EPI images were collected using a Bruker 4T (Siemens Syngo console, TR: 2s, TE: 30ms, matrix: 64x64, 24 slices, voxels: 3.8x3.8x4.0 mm). Subjects performed a continuous performance task in which 3 digit numbers were presented. Images were preprocessed in SPM5 and DCM was conducted on time series from the ACC, DLPFC, superior parietal cortex, the caudate nucleus, and the visual cortex. We looked for instrinsic connection strengths, task modulation of

instrinsic connections, and driving inputs into regions.
Results: Intrinsic connections of schizophrenia offspring are different from healthy controls. SCZ_{off} showed reduced ACC-Caudate coupling but increased ACC-DLPFC coupling. Increases in task dependent modulation of the ACC-parietal pathway was also observed in SCZ_{off}.
Conclusions: Control mechanisms play an important role in functional integration of tasks. SCZ_{off} demonstrate imbalances and inefficiencies in the interaction between brain regions. Reduced ACC-Caudate coupling may demonstrate impairments in neural transmission. By contrast, ACC-DLPFC coupling and modulation of the ACC-Parietal pathway reflects inefficiently increased control by the ACC. The combination of fMRI and DCM may enhance understanding of brain development.

252. The Backward Masking Red Light Effect in Schizophrenia: Relationship with Symptoms and Premorbid Intelligence Estimate

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Background: The "backward masking red light effect" involves a change in visual backward masking accuracy with a red (compared to green) background that is in the opposite direction as that found with nonpsychiatric controls. This effect has been reported in individuals with schizophrenia, their first-degree relatives, and a schizotypy sample. The current study examines the relationship of this effect with symptom and premorbid intelligence measures in a new sample of outpatients with schizophrenia, and adds a new comparison color background.
Methods: A location backward masking by pattern task was administered to 16 outpatients with schizophrenia and 21 nonpsychiatric controls. The task was presented on red, green, and gray backgrounds.
Results: Results revealed an interaction for group x color x SOA. At the 60 ms SOA, participants with schizophrenia tended to decrease accuracy with a red (compared to gray) background, while controls tended to increase accuracy. This effect was correlated with an increase in negative symptoms, $r(16) = -.60$, $p = .02$, and a lower premorbid estimate of IQ, $r(16) = .56$, $p = .02$.
Conclusions: These findings replicate the earlier report of the red light effect in an inpatient schizophrenia sample, but found that within the current study, this effect was stronger with a gray background contrast (instead of green). The current study is also the first to show that this effect is related to a greater degree of negative symptoms and a lower estimated premorbid IQ. This effect continues to show promise as a novel qualitative endophenotype for schizophrenia.

253. Effect of Comt Val108/158Met Genotype on Different Executive Functions in Patients with Schizophrenia

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Background: Recent evidences suggest cognitive disturbance as a core feature of schizophrenia. Executive functions (EF) are a set of cognitive abilities that control and regulate other abilities and behaviors and are necessary for goal-directed behavior. The catechol O-methyltransferase (COMT) is an enzyme involved with dopamine catabolism and has a particular role in prefrontal cortex function where dopamine transporter is less abundant. A functional COMT polymorphism (Val108/158Met) has been associated with both increased susceptibility for schizophrenia and EF performance. However, most of these studies consider EF as an unitary concept, while, in fact, encompass different sub-domains. The present study aimed to examine COMT Val/Met genotype as a predictor of two more basic EF (shifting and updating), and a cognitive complex task.
Methods: 85 schizophrenic patients were recruited from an outpatient clinic. Each patient was assessed and diagnosed by two psychiatrists according to DSM-IV. COMT Val/Met genotype was determined as a restriction fragment length polymorphism after polymerase chain reaction amplification and digestion with *Nla*III. Neuropsychological tasks were Trial Making Test, Keep Tracking Task, Digit Span Task, and Tower of London.
Results: Analyses of covariance, having intelligence as a covariant, showed that carriers of Met allele (in homo or heterozygosis) presented superior performance on shifting and updating. Performance on complex cognitive task did not reach significant difference between groups.
Conclusions: The present study suggests that polymorphism of COMT may influence differently the level of cognitive processes related to EF. Further studies with larger samples should be conducted to confirm these findings.
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254. Modeling Cognitive Phenotypes from Circuit to Syndrome

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Background: Bioinformatics strategies are under development to leverage knowledge about gene expression and biological pathways that may help constrain genetic hypotheses, but so far the links of these resources to higher phenotypic levels are rudimentary.
Methods: The Consortium for Neuropsychiatric Phenomics (CNP) at UCLA is developing strategies to help investigators model hypotheses spanning genetic, proteomic, cellular systems and signalling pathways, neural systems, cognitive, symptomatic and syndromal levels. The CNP is focused on cognitive phenotypes that include "response inhibition" and "memory/working memory" phenotypes as series of multi-level, directed acyclic graphs. These graphs provide a framework for formalizing hypotheses about neural circuits cognitive mechanisms, the links of cognitive deficits to symptoms and diagnostic categories, and modelling of cognitive constructs with respect to the observable test variables that are used to measure these. Nodes and edges support qualitative and quantitative annotation, so that relations among entities can be expressed with rich context and linked to PubMed queries to generate automatic literature retrieval pertinent to the hypotheses of interest.
Results: We present proof-of-concept representations of response inhibition (RI) and working memory (WM) mechanisms incorporating neural circuitry and selected annotations and evidence-based "assertions" including modelling effects of diagnostic groups, relations to symptoms, and relations to cognitive phenotypes.
Conclusions: These graphical representations provide context, and illustrate the complexity of multi-scale hypotheses that aim to test effects of genetic variation on complex behavioral functions. These initial efforts highlight the need for improved mechanistic modelling and increased precision in the specification of hypotheses about candidate genes in order for these hypotheses to be testable.
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255. Dissociative Symptoms and Interregional EEG Cross-Correlations in Paranoid Schizophrenia

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Background: Recent findings indicate that binding and synchronization of distributed activities are crucial for the mechanism of consciousness and there is increased evidence that disrupted feature binding produces disintegration of consciousness in schizophrenia. These data suggest that the disrupted binding and disintegration of consciousness could be related to dissociation, which is historically linked to Bleuler's concept of splitting in schizophrenia.
Methods: In the present study we aimed to investigate relations among EEG activities of cortical sites and used psychometric measures of positive and negative schizophrenia symptoms (PANSS) and Dissociative Experiences Scale (DES) in 58 patients with paranoid schizophrenia.
Results: The results show statistically significant Spearman correlations of DES with cross-correlation function in 9 (of 16) EEG pairs (R from -0.273 to -0.393, $p<0.05$). Positive symptoms display significant Spearman correlation with mean of cross-correlation function only in 1 EEG pair (F4-C4, R= -0.343, $p<0.05$). Results of Mann-Whitney test between patients with higher (DES<30) and lower dissociation show statistically significant differences between the groups for cross-correlations in 9 EEG pairs.
Conclusions: Results of this study provide first supportive evidence for negative relationship between cross-correlation indices and symptoms of dissociation in schizophrenia.
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256. Psychopathological Symptoms and Neurocognitive Tets Performance in Polish 1200 Schizophrenic Patients Treated with Olanzapine (Olzapin)

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Background: Cognitive dysfunctions in schizophrenia show an association with negative symptoms and brain abnormalities. Studies on correlations between psychometric ratings and cognitive functions in schizophrenic patients revealed inconsistent results and therefore assessment in both cross-sectional and longitudinal surveys has been suggested. The aim of the study was to assess the correlation between PANSS scale and performance on cognitive tests in a cohort of schizophrenic patients treated with olanzapine (Olzapin) for at least one month.
Methods: Patients with the ICD-10 diagnosis of schizophrenia treated with efficacious dose of olanzapine were enrolled in 38 centres in Poland. Neuropsychological testing was based on short computerized battery which consisted of five tasks: simple reaction time test (SRT), Verbal Memory Test (VM), GoNoGo test (GNG), Stroop Test (STR) and Visual Working Memory Test (VWM). On the same day an assessment of psychopathology with the PANSS was performed. Advanced multidimensional data analysis, (i.e. Principal Component Analysis and Artificial Neural Networks methods), were used in statistical analysis.
Results: Overall 1200 patients aged 18-53 (mean 43,7) years were enrolled. Duration of the illness was 1-15 years (mean 8±6). The average dose of olanzapine was 10,5±6 (5-25) mg/day. Mean intensity of PANSS total was 70±17. Reaction time, visual memory, GoNoGo test and Stroop test performance were associated with intensity of both positive and negative symptoms on PANSS scale.
Conclusions: Most cognitive measures were correlated with the intensity of negative symptoms on PANSS scale, and this indicates strong association between negative symptoms and cognitive impairment in the majority of domains.
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257. Cannabis Use is Associated with Greater Prepulse Inhibition in Normals, Prodromal and First Episode Psychosis Patients

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Background: The observed association between cannabis and psychotic illness has lead to translational studies that investigate the role of cannabinoid receptors and endocannabinoids in dopamine regulation and the pathophysiology of schizophrenia. Prepulse inhibition (PPI) is deficient in schizophrenia spectrum illness and in animals exposed to dopamine agonists and NMDA antagonists. Developmental manipulations including isolation rearing and chronic pubertal cannabinoid administration also disrupt PPI in adult animals. Of the few PPI/cannabis studies done in humans, one reported no difference in PPI in chronic cannabis abusers while another showed deficits in a PPI attentional paradigm. Other studies have explored the possible role of cannabinoids in the treatment of psychosis given the potential protective effects of anandamide in early psychosis. Testing this hypothesis, PCP exposed rats demonstrated improved PPI after self administration of cannabinoids while administration of cannabidiol also increased PPI in mice.
Methods: PPI was assessed in 71 normals, 80 at risk for psychosis (putatively prodromal) and 63 early episode psychosis patients. 106 subjects had never used cannabis while 108 reported a cannabis use history.
Results: There were no significant group or interaction effects but there was a significant effect of cannabis on PPI.
Conclusions: Cannabis use history was associated with greater levels of PPI in normals and individuals in the early phase of psychotic illness. It is not possible to determine whether cannabis use increased PPI given the study design but this observation does suggest that future work is needed to assess potential therapeutic benefits of cannabinoids in early psychosis.
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258. Impact of Neurocognition on Social and Role Functioning in the Prodromal Phase of Schizophrenia

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Background: Neurocognitive impairments have been shown to be related to functioning in schizophrenia. Early evidence from the RAP Program has found that neurocognitive impairments also are present in the prodromal period of schizophrenia. We examined the extent to which such deficits impact functioning in a sample of treatment-seeking individuals considered to be prodromal or at Clinical High-Risk (CHR) for psychosis.
Methods: The Recognition and Prevention Program (RAP) in New York is a longitudinal study of adolescents (12-22 years-old) considered prodromal for schizophrenia. The current sample consists of healthy controls (n=88) and patients meeting criteria for CHR (n=127) based on the presence of moderate

to severe attenuated positive symptoms that are below psychotic intensity. At baseline, subjects received a comprehensive battery that consisted of 18 neuropsychological tests assessing 8 domains of neurocognitive performance. Functioning was assessed with the Global Functioning: Social and Role Scale developed as part of the RAP Program.

Results: Relative to controls, patients showed significant neurocognitive deficits, mainly in the domains of Verbal Memory (p<.001), Executive Function (p<.001), and Processing Speed (p<.001). Social (p<.001) and role (p<.001) functioning are also impaired in the prodrome. Linear regression analyses indicated that processing speed scores were poorer in those with lower social (R^2=.10, p<.001) and role (R^2=.08, p<.001) scores.

Conclusions: Clinical high-risk subjects showed significant impairments in neurocognition and functioning. We conclude that functional impairments are already detectable in the schizophrenia prodrome prior to the onset of psychosis and processing speed appears to be an important cognitive predictor of poor functioning.

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259. COMT Influences on Prefrontal and Striatal Bold Responses During Working Memory Among Individuals with Schizophrenia, Their Siblings and Healthy Controls

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Background: The polymorphism Val158Met from the COMT gene has received a good deal of attention with regard to its role as a putative risk gene for schizophrenia. Its role in schizophrenia pathology is thought to be related to the impact expression at this allele has on dopamine availability, particularly in the prefrontal cortex. Given evidence for cortico-striatal interactions, COMT may also impact dopamine tone and activation subcortically. How the influence of COMT variation on sub cortical functioning in schizophrenia is not yet known.

Methods: In the current study, patients with schizophrenia, their well siblings, and healthy controls were genotyped for the Val158Met polymorphism. Participants were scanned using functional Magnetic Resonance Imaging (fMRI) while they performed verbal and non-verbal working memory tasks. Participants also completed battery of tests that assessed a range of cognitive domains and symptom categories.

Results: During the verbal working memory task, the Val allele in the patient and sibling groups was associated with increased activity of the DLPFC, striatum, and the cerebellum. Val homozygote performed worse than Met carriers cognitively, but particularly so on a measure of IQ and in the domain of executive functioning. Val homozygotes also displayed higher negative symptoms, however patient Met carriers displayed higher positive symptoms.

Conclusions: Our findings support and extend previous studies of COMT effects on cognition and schizophrenia expression, and implicate COMT involvement in cortico-striatal interactions in schizophrenia.

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260. Stability, Diagnostic Specificity and Genetic Liability for Context-Processing Deficits In Schizophrenia

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Background: Context-processing deficits have been shown in schizophrenia during first-episode, medication-naïve status, that persist after short-term antipsychotic treatment and in first-degree relatives. To confirm longer term stability of deficits, we examined schizophrenia (SZ) patients during first-episode, medication-naïve status through to one-year follow-up, compared to healthy control (HC) and psychosis comparison (PC) groups. We also conducted a direct comparison the performance in first-degree relatives to these other groups at baseline.

Methods: 36 HC, 28 SZ, 14 PC and 31 first-degree relative participants performed a version of the AX-CPT (Continuous Performance Test) at index (for SZ and PC, first-episode psychotic, medication-naïve status), 8 weeks, 6 months, and at 1 year (relatives only at baseline). Reaction time, error rates and signal detection indices (d') of context processing were analyzed. Linear discriminant analyses (LDA) on early timepoints (baseline, 8 weeks) were conducted to predict confirmatory diagnosis (SZ vs. PC) at 6 months.

Results: SZ showed significantly worse context-processing performance than HC or PC at both baseline and at one-year followup. First-degree relatives showed deficits that were intermediate to the SZ and HC groups. LDA showed classification rates of 67%.

Conclusions: Our results suggest that context processing deficits in schizophrenia show diagnostic specificity and stability after one year of treatment. First-degree relatives showed significant, but more moderate deficits. Classification analyses showed that context-processing performance had moderate success at discriminating schizophrenia vs. other psychotic disorders. Together, these results indicate that context-processing impairments in schizophrenia are stable, index genetic liability, and can have utility in diagnostic classification.

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261. Intra-Individual Variability Across Neuropsychological Tasks in Schizophrenia: Its Relationship to Disease Status and Functioning

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Background: During the course of neuropsychological testing, most individuals' performance is somewhat variable - meaning that performance is likely to vary to some degree across different testing sessions, neuropsychological tasks, or trials of the same task. Recently, however, greater degrees of intra-individual variability (IIV) have been linked to impaired cognitive functioning and disrupted neurobiology.

Methods: Schizophrenia patients (N = 422), their unaffected siblings (N = 436), and healthy volunteers (N = 372) completed a battery of neuropsychological tests. These results were factor-analyzed in previous work, yielding six factor-based composite scores: verbal memory, NBack, visual memory, processing speed, card sorting, and span. For each participant, we calculated a standard deviation representing the individual's performance variation across these composites, which served as our IIV statistic.

Results: IIV was significantly more pronounced in schizophrenia probands than in siblings, and was least pronounced in controls; the association of group membership with IIV remained significant even after controlling for demographic covariates and mean performance on all tasks ($F(2, 1218) = 10.493$, $p < .001$; post hoc two group contrasts, $p < .01$ for each). Furthermore, both across groups and within the patient group, IIV was negatively associated with various indicators of daily functioning and community status.
Conclusions: Across-task IIV accounts for variation in cognitive performance and functional status among schizophrenia patients, their siblings, and controls that is not accounted for by mean level of performance. Indexes of intra-individual variability may represent useful additions to investigations of cognitive performance in schizophrenia.
Supported by Intramural Research Program, National Institutes of Health

262. Abnormal Early and Late Selective Attention Related ERPs in Subjects at Familial Risk for Schizophrenia

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Background: Previous research has documented attention disturbances at all levels of information processing in schizophrenia. Despite the fact that these deficits are thought to underlie global cognitive and social dysfunction, the biological basis of attention deficits in schizophrenia remain poorly understood.
Methods: Event-related potentials (ERPs) and brain oscillatory activity were assessed in 15 patients with recent-onset schizophrenia, 15 subjects at familial risk for schizophrenia, and 15 healthy comparison subjects. Electrophysiological recordings were obtained while subjects performed a visual choice response target detection task. Stimuli consisted of four letters (H, E, L, P) and four numbers (8, 3, 7, 9) in two sets (red or green). Subjects were instructed to respond with their middle finger to a target stimulus, identified by a category and a color (e.g. red letters), and to respond with their index finger to all other stimuli.
Results: Preliminary ERP results indicate significant group differences in both the early frontal selection positivity and the late P3 ERP component in response to color-relevant non-target and target stimuli respectively.
Conclusions: The results suggest that the observed deficits in early sensory and in later executive attentional ERPs may serve as biological markers of risk and/or diagnostic tools for schizophrenia. Longitudinal analyses will further assess their predictive value for illness onset in populations at risk for psychotic illness. Future study plans include to increase the sample sizes and to further characterize the relationships between EEG/ERP abnormalities and various neurocognitive and clinical measures.
Supported by NIH

263. Interhemispheric Integration in Schizophrenic and Bipolar Patients: A Study with the Redundant Signal Effect

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Background: From the study of scientific literature it can be learnt that in psychotic patients there are abnormalities in interhemispheric interactions. A reliable behavioral measure of interhemispheric integration of visual stimuli is the Redundant Signal Effect (RSE), that is, the speeding of responses of double stimuli presented across the vertical meridian as compared to single stimuli in one hemifield.
Methods: In a first experiment 18 schizophrenic patients and 18 matched controls had to press as quickly as possible the space-bar of a PC keyboard with the index-finger of their right or the left hand, following unstructured single, simultaneous bilateral and asynchronous double stimuli (InterStimulus Interval-ISI: 17, 51, 68 ms). In the second experiment a different group of 18 bipolars and 17 matched controls performed the same task.
Results: In the 1st experiment, schizophrenic patients reacted reliably faster to simultaneous double (392 ms) than to single stimuli (417 ms) with a RSE of 25 ms. There was no significant effect for asynchronous double stimuli. In the 2 nd experiment bipolar patients reacted reliably faster to simultaneous double (339 ms) than single stimuli (366 ms), with a RSE of 27 ms. For asynchronous double stimuli there was a significant RSE at ISI 17 (16 ms) and at ISI 68 (9 ms).
Conclusions: We found that schizophrenic and bipolar patients have an enlarged Redundancy Gain with respect to controls. This suggests that there is an impairment of the integration of informations between the cerebral hemispheres. In bipolar patients there is a significantly larger RSE in two conditions (ISI 17 and 68); in schizophrenic patients the RSE disappear at ISI 17 ms, while it is still present in controls.
The work is still in progress because further researchs are needed to better understand the difference between the two groups of patients.

264. Cerebellar Timing Dysfunction in Schizotypal Personality Disorder: Eyeblink Conditioning as a Potential Biomarker for Schizophrenia

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Background: Accumulating evidence suggests that abnormalities in neural circuitry and timing associated with the cerebellum may play an important role in the pathophysiology of schizophrenia (SZ). Schizotypal personality disorder (SPD) is thought to be an intermediate phenotype of SZ, but individuals with SPD are freer from potential research confounds such as long-term medication, recurrent hospitalization and prolonged functional impairment. This subject group may therefore offer insight into biobehavioral correlates of schizophrenia.
Methods: The present study employed a delay eye-blink conditioning (EBC) paradigm to examine cerebellar timing circuits in SZ, SPD and Control subjects ($n = 19$ per group) that were matched on age and sex. Correlates between EBC and neuropsychological function using the picture completion, digit symbol coding, similarities and digit span subscales of the WAIS were also investigated.
Results: The SZ and SPD groups demonstrated robust impairments in EBC relative to the control group; they had significantly fewer percent CRs, as well as smaller CR amplitudes with earlier peak CR latencies. Medication status did not significantly affect these results. Impaired EBC performance was significantly associated with decreased processing speed in digit symbol coding in the schizophrenia spectrum group.
Conclusions: These findings suggest that eyeblink conditioning may be a potential biomarker for schizophrenia and support the role of altered cortico-cerebellar-thalamic-cortical (CCTC) circuitry in the pathophysiology of schizophrenia.
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265. No Influence of Age at Onset and Duration of Illness on Executive Functioning Among Patients with Schizophrenia

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Background: Cognitive impairment is considered a core feature of schizophrenia. Several studies have investigated the relationship of age at onset with clinical presentation and cognitive performance of schizophrenic patients. Indeed, there are a lot of evidences that age at onset has clear impact on clinical manifestations and neuropsychological profile of disease. Duration of illness and ageing are other variables related to cognitive outcome of patients. The relative contribution from each of these variables on different aspects of executive functions is still controversial. The aim of this is study was to investigate the relative impact of age at onset and duration of illness on different abilities related to executive functions.
Methods: 84 schizophrenic patients were recruited from UNIFESP Schizophrenia Program. Each patient was assessed and diagnosed by two psychiatrists according to DSM-IV. Neuropsychological tests were Trial Making Test, Visual Working Memory (VWM), Digit Span Task, and Tower of London. Variables were tested and met normal distribution conditions. A linear regression analyses was conducted considering neuropsychological measures as dependent measures and onset and duration of illness as independent measures.
Results: It was not observed statistical significance on any cognitive function measured. However, age at onset and duration of the illness explained together 37% of variability of VWM, although not reaching statistical significance (t=-1,33; $p = 0,11$).
Conclusions: These findings confirmed previous studies that found that cognitive deficits are relatively stable through duration of illness, even when different cognitive abilities related to executive functions are considered. The impact on VWM should be further investigated.
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266. Attentional Load and Visual Gamma Oscillations in Schizophrenia

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Background: Previous research has shown that the early visual-evoked gamma oscillation (Vg1) of the EEG is reduced in chronic schizophrenia patients (SZ) compared with healthy control subjects (HC) in visual discrimination tasks. Here we investigated whether the Vg1 deficit in schizophrenia is modulated by attentional load.
Methods: Subjects (14 HC, 23 SZ) discriminated between a target disc (20% occurrence) and a standard disc (80% occurrence). Attentional load was manipulated by varying the discs' size difference: large (Easy condition), medium (Medium), or small (Difficult), in three counterbalanced blocks. The oscillations evoked by the standard stimuli were measured using the Morlet wavelet transform.
Results: Subjects' discrimination performance decreased as task difficulty increased. HC and SZ did not differ in performance. Vg1 (70-115 ms, 32-50 Hz) was observed in both HC and SZ and did not differ between groups, nor was it modulated by attentional load. A later visual-evoked gamma oscillation (Vg2: 173-261 ms, 23-39 Hz) was reduced in SZ compared to HC. Statistical time-frequency mapping revealed that attentional load increased beta activity (240-300 ms, 18-20 Hz) in frontal, parietal, and occipital sites in HC, but not SZ.
Conclusions: The Vg1 deficit was not found, indicating that this deficit is not general, but a later visual-evoked gamma oscillation deficit was observed. Neither visual-evoked oscillation was modulated by attentional load. Instead, attentional load effects were manifested in HC as beta activity over cortical areas involved in attentional control. This beta activity was absent in SZ, consistent with the attentional control deficits in this disorder.
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267. Relationship between Steady-State Gamma Driving and Cognitively Elicited Gamma Frequency Responses in Schizophrenia

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Background: Auditory evoked gamma band responses (GBRs) are reduced in schizophrenia patients (SZ) on many tasks. The current study evaluated the functional specificity and inter-relationships of gamma deficits on three different auditory paradigms.
Methods: EEG was recorded from 51 SZ and 34 healthy comparison (HC) subjects during a 40-Hz binaural click train task, an oddball task, and a paired click paradigm. The steady-state auditory evoked potential (SSAEP), early auditory GBRs (EAGBRs) to oddball target and standard stimuli, and EAGBRs to both S1 and S2 clicks were analyzed respectively for each paradigm. Time-frequency spectral analysis was used to extract phase locking factor (PLF) and evoked power measures.
Results: SZ had reduced PLF compared with HC in the 40-Hz SSAEP ($p< .01$). In the oddball task, patients had reduced EAGBR evoked power to standard stimuli ($p< .05$), and reduced PLF ($p< .05$) and evoked power ($p< .01$) to target stimuli. In the paired click paradigm, patients had reduced EAGBR evoked power ($p< .01$) and PLF ($p=.01$) to S1 stimuli, and reduced PLF ($p< .01$) to S2 stimuli. Age-of-onset was significantly associated with gamma measures. EAGBR measures to S2 click stimuli were associated with SSAEP activity ($r=.32$; $p=.05$) and with oddball standard stimuli EAGBR evoked power ($r=.44$; $p<.01$).
Conclusions: Deficits in GBRs in SZ are not strictly task-specific, with shared variance between EAGBRs to S2 clicks and some other measures, but not between oddball EAGBRs and SSAEP measures. The common and independent pathophysiological mechanisms underlying these results remain to be determined.
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268. Emotional Interference Effects during Voluntary Attention in Individuals with Schizophrenia and Familial High Risk

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Background: Schizophrenia is associated with changes in both attention and social-emotional processing. It has been suggested that prior to the onset of psychosis, individuals with schizophrenia may show an "over-evaluation" of task-irrelevant but emotionally salient information at the expense of goal-

relevant stimuli. However, it is unclear whether these changes are apparent in individuals with familial high risk (FHR), potentially reflecting a vulnerability marker for schizophrenia. The goal of this study was to examine the neuroanatomical basis of attention deficits and emotional interference in individuals with schizophrenia and FHR.
Methods: Functional MRI was used to examine attention and emotional interference effects in 14 individuals with schizophrenia, 19 with FHR, and 17 controls. Participants performed an emotional oddball task requiring selective attention to task-relevant targets (pictures of animals) among a series of frequent scrambled images and rare task-irrelevant emotional and neutral pictures.
Results: During attention to task-relevant targets, the group with schizophrenia showed significantly reduced prefrontal, caudate, and cingulate activation relative to controls. The FHR group showed reduced activation in the cingulate, insula and temporo-parietal areas. During processing of task-irrelevant emotional stimuli, the group with schizophrenia showed reduced activity in the inferior frontal cortex and caudate. In contrast, the FHR group showed increased activation in the amygdala, orbitofrontal cortex and inferior frontal cortex relative to controls.
Conclusions: The results suggest that changes in fronto-limbic circuitry may reflect a potential vulnerability marker for schizophrenia, with activation patterns suggesting increased processing of task-irrelevant emotional stimuli in individuals with FHR.
Supported by R01MH058251-08

269. The Course of Neuropsychological Performance and Functional Capacity in Older Patients with Schizophrenia: Influences of Previous History of Long-Term Institutional Stay

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Background: Chronically institutionalized patients with schizophrenia have been reported to manifest cognitive and functional decline in late life. Previous studies were limited by the fact that current environmental influences could not be separated from life-time history of illness. The present study examined older outpatients who varied in their lifetime history of long-term psychiatric inpatient stay.
Methods: Community dwelling patients with schizophrenia (n=111) and healthy comparison subjects (n=76) were followed up over periods from 18 to 45 months. They were examined two or more times with a neuropsychological (NP) assessment battery and performance-based measures of everyday living skills (UCSD Performance-based skills assessment; UPSA) and social competence. A mixed-effects model repeated-measures method was used to examine changes in performance over time.
Results: There was a significant effect of longest institutional stay on the course of the UPSA, with this effect significant at a trend level for social competence and nonsignificant for NP performance. When the schizophrenia patients were divided on the basis of median length of institutional stay (6 months) and compared to healthy comparison subjects across the three assessments, patients with longer institutional stays worsened on the UPSA while patients with shorter lifetime stays manifested a practice effect. Similar findings were detected for the social competence measures. For NP performance, both patient samples showed modestly lower scores, while the HC group manifested a practice effect. Reliable change index (RCI analyses) indicated that worsening on the UPSA for longer stay patients was significantly more likely than improvement with the reverse true for shorter stay patients.
Conclusions: Life-time history of institutional stay was associated with deteriorated functioning over time on measures of social and everyday living skills. NP performance on the part of people with schizophrenia did not evidence the practice effect seen in the HC sample. These data suggest that schizophrenia patients with a history of long-term institutional stay may worsen in some ability areas even if they are no longer institutionalized.
Supported by RO1 MH63116; NIMH

270. Impairment of Executive and Storage Aspects of Spatial Working Memory in Patients with Schizophrenia and Their First-Degree Relatives

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Background: Working memory (WM) impairment is a promising candidate endophenotype for schizophrenia. The identification of whether certain aspects of WM dysfunction (maintenance or manipulation) are differentially impaired in patients with schizophrenia and their first-degree relatives could inform the search for schizophrenia susceptibility genes.
Methods: A previously validated spatial WM paradigm contrasting maintenance-only and maintenance-and-manipulation processes was assessed in a sample of 60 patients with schizophrenia, 107 first-degree relatives, and 123 comparison control subjects from the UCLA Family Study. Multivariate mixed model analyses were conducted, controlling for age and gender, in order to determine whether patients with schizophrenia demonstrate differential effects in component WM subprocesses while accounting for dependency of observations within families. Appropriate follow-up tests were performed.
Results: Findings indicated that schizophrenia patients are consistently impaired on WM tasks, irrespective of processing requirements (p's < .001). Schizophrenia probands, first-degree relatives, and control subjects showed lower performance, to equivalent degrees, on WM tasks requiring simultaneous maintenance and manipulation of information compared to maintenance-only tasks. Simple effect analyses revealed that patients' relatives performed more poorly than control subjects on both tasks, but the difference was significant only for WM task with more demanding central executive processing requirements ($p < .05$). Results were equivalent when controlling for reaction time.
Conclusions: Along with evidence that WM abilities are substantially heritable, the current results support the validity of impairment in manipulation of information in spatial WM as an endophenotype for schizophrenia in large-scale clinical genetic studies of schizophrenia.
Supported by National Institute of Mental Health

271. Cortical Inhibition and Working Memory in Schizophrenia: A TMS/EEG Study

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Background: Research has implicated deficient cortical inhibition (CI) in the dorsolateral prefrontal cortex (DLPFC) as a potential mechanism underlying the working memory (WM) impairments observed in schizophrenia. The aim of this study was to compare CI in the DLPFC of patients with schizophrenia to a group of healthy controls and investigate the relationship between CI and WM performance.

Methods: CI was assessed in the DLPFC of 11 patients with schizophrenia and 11 healthy participants using paired pulse Transcranial Magnetic Stimulation (TMS) and electroencephalography. CI was examined using long interval cortical inhibition (LICI), which involves the application of a conditioning stimulus (CS) followed by a test stimulus (TS). Seventy five single (unconditioned stimulus) and 75 paired pulses (conditioned stimulus) with an inter-stimulus interval of 100 ms were randomly applied to each DLPFC at a frequency of 0.2 Hz. A *n*-back task was used to assess WM capacity.
Results: Patients with schizophrenia demonstrated significantly less suppression in mean cortical evoked activity following ppTMS to the left DLPFC than healthy controls. A significant positive correlation between percentage LICI and WM performance was also observed.
Conclusions: The data obtained in the present study provides convincing preliminary evidence suggesting that abnormal GABAergic inhibitiory neurotransmission may represent an important neurophysiological process underlying the WM deficits observed in schizophrenia.
Supported by National Health and Medical Research Council: Practitioner Fellowship (PF)

272. Differences in Frontal Activation in Adult Patients with Schizophrenia and in Psychotic Adolescents with Schizophrenic Symptoms in Two Fmri Tasks.

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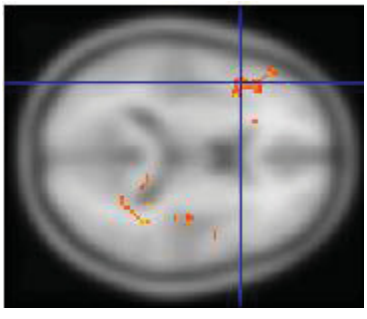
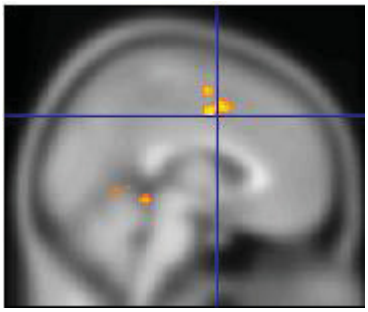
Background: Language processing abnormalities and inhibition difficulties are hallmark features of schizophrenia. The objective of this study is to asses the blood oxygenation level-dependent (BOLD) response at two different stages of the illness and compare the frontal activity between adolescents and adults with schizophrenia.
Methods: 10 adults with schizophrenia (mean age 31,5 years) and 6 psychotic adolescents with schizophrenic symptoms (mean age 16,2 years) underwent functional magnetic resonance imaging while performing two frontal tasks. Regional activation is compared in the bilateral frontal areas during a covert verbal fluency task (letter version) and a Stroop task (inhibition task).
Results: Preliminary results show poorer task performance and less frontal cortex activation during both tasks in the adult group of patients with schizophrenia. In the adolescent patients group, fMRI analysis show significant and larger activity in the left frontal operculum (Broca's area) in the verbal fluency task and greater activity in the medium cingulate during the inhibition phase of the Stroop task.
Conclusions: These preliminary findings suggest a decrease of frontal activity in the course of the illness. We assume that schizophrenia contributes to frontal brain activity reduction.



Difference of activation between adolescent and adult patients with schizophrenia during a verbal fluency task : adolescents show larger activity in the left frontal operculum (Broca's area)



Difference of activation between adolescent and adult patients with schizophrenia during the inhibition phase of the Stroop task : adolescents show larger activity in the medium cingulate

273. Generalized Enhancement of Episodic Memory by Prior Reward Experience

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Background: With event-related fMRI we have previously demonstrated reward-driven correlations between the VTA and hippocampus and enhanced memory for upcoming events. These findings are consistent with the hypothesis that reward motivation promotes memory formation via dopamine release in the hippocampus prior to learning. This study characterizes the temporal duration of memory enhancement following reward anticipation.
Methods: To determine the effects of frequent rewards that occur prior to and separate from encoding, participants (n=10) performed a rewarded cued reaction time task for several minutes before they were presented with a series of scene photographs (reward context). The same subjects also performed a non-rewarded cued reaction time task before they were presented with a separate series of scene photographs. Recognition was tested the following day. To determine whether memory effects were purely due to increased arousal, a separate group of participants (n=9) performed similar tasks, except that instead of receiving frequent rewards during the active condition they experienced unpredictable aversive noises while performing a non-rewarded cued reaction time task (aversive arousal context).
Results: Recognition memory was higher for images seen in the reward context, and this increase was driven by an increase in high confidence responses ($t(9)=2.06$, $p=0.04$; two-tailed, paired). There was no such change in the aversive arousal context ($t(8)= 0.13$, $p=0.90$; two-tailed, paired).
Conclusions: These results suggest episodic memory can be enhanced by exposure to frequent rewards prior to encoding, and increased arousal alone does not seem to account for these effects.
Supported by NARSAD

274. Attention Modulation of Sensory Processing: an fMRI Study

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Background: Attention systems in the brain play a top-down modulatory role affecting how sensory cortices respond to stimuli. This is clinically important, as uncontrolled processing of context-irrelevant sensory stimuli is a

common feature of neuropsychiatric disorders and may contribute to multiple abnormalities including hallucinations. Studies examining how parametric modulation of attentional demands affects processing of task-irrelevant information both within-mode (e.g., visual information during a visual task) and cross-mode (auditory information during a visual task) have not been conducted.
Methods: To test the hypotheses that increasing attentional demand diminishes cortical response to irrelevant sensory information, we conducted fMRI studies with healthy subjects performing a visual attention task with three levels of attentional load. Task-irrelevant stimuli were added while this task was performed: either visual motion was added to the periphery of the visual field or pure tones were played binaurally.
Results: As predicted, as the attention load of the primary task increased, the medial temporal area, a primary visual motion processing center, showed progressively reduced activation to the irrelevant motion, and medial superior temporal cortex (primary/secondary auditory cortex) showed a similar reduced activation to the irrelevant auditory information.
Conclusions: These data provide insight into top-down regulation of basic sensory processing and are novel in their demonstration of intra- and cross-modal attentional modulation. These paradigms may be useful for studying psychotic features such as hallucinations, which are poorly understood in terms of neural systems mechanisms but may result from reduced top-down attentional control leading to failure to suppress irrelevant sensory information.
Supported by NARSAD

275. Emotion Processing Impairment in Youths At-Risk for Psychosis

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Background: Neurodevelopmental abnormalities affecting behavior are present in children at-risk of developing psychosis long before the onset of illness. Cognitive abilities, including neurocognition and social cognition, are extensively implicated in schizophrenia and may represent candidate endophenotypes. Impaired endophenotype performance in adolescents deemed at-risk for schizophrenia is a characteristic reflecting the endophenotypes ability to serve as a marker for early identification and treatment.
Methods: Youths (ages 14-25) completed a comprehensive diagnostic assessment and the University of Pennsylvania Computerized Neurocognitive Battery, which includes tests of emotion identification (ER40) and emotion differentiation (EmoDiff), and other studies. Groups included individuals deemed at-risk for psychosis [Genetic risk (GR): family history of schizophrenia, n=52; Clinical Risk (CR): prodromal symptoms but no family history, n=17]; schizophrenia (SZP): n=77; and healthy controls (CNT), n=94.
Results: On ER40, youths with SZP and those at-risk compared to CNT showed impairments in overall (SZP:p<001, at risk:p<.010), happy (SZP:p=020), sad (SZP:p=021), anger (SZP:p=005, at risk:p=.008) and fear (SZP:p=016, at risk:p=.05) identification. On EmoDiff, youths with SZP compared to CNT showed impairments in happy (p<.001)and sad (p=.037) differentiation, while performance of at-risk youth was intermediate.
Conclusions: Tests of emotion processing revealed that at-risk youth showed decreased performance similar to young persons with schizophrenia. Processing of facial affect may represent an endophenotypic marker and reflect pathophysiological abnormalities involved in the development of schizophrenia.
Supported by K08MH79364

276. Schizophrenia-Like Cognitive Control Deficits in First Episode Bipolar Disorder with Psychotic Features

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Background: Cognitive control deficits are consistently documented in patients with chronic and first-episode schizophrenia (SZ), and are distinct from those seen in patients with unipolar depression or stable bipolar (BP) illness without psychosis. However, it remains unclear to what extent BP patients with psychosis show similar control deficits to individuals with schizophrenia. First-episode SZ, first-episode BP with psychotic features, and healthy control (HC) participants completed a computerized cognitive control measure (AX-CPT). We hypothesized that BPs would show AX-CPT deficits compared to HCs, but would have less severe deficits than SZs.
Methods: BP (n=11), SZ (n=20), and HC (n=20) participants were identified from referrals to the UC Davis Early Detection and Preventative Treatment (EDAPT) clinic, using the Structured Interview for Prodromal Syndromes (SIPS) and Structured Clinical Interview for DSM-IV (SCID-I/P).
Results: BPs showed a specific deficit in cognitive control as measured by lower signal detection ($p<0.05$) and BX trial accuracy ($p<0.05$) compared to HCs. SZs also demonstrated lower performance than HCs on these measures ($p<0.01$). However, there were no differences between SZ and BP performance.
Conclusions: Bipolar individuals with psychotic features show cognitive control deficits similar to those seen in schizophrenia, suggesting that cognitive control impairment may represent a shared cognitive feature of these disorders. Future work will investigate whether presence of psychotic symptoms and phase of illness in bipolar individuals is associated with cognitive control deficits and dysfunctional recruitment of prefrontal regions (e.g., DLPFC). Results from an expanded sample will be presented.
Supported by 5RO1MH059883

277. Automatic Semantic Activation in Schizophrenia: A Masked Priming Study

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Background: Automatic semantic priming may be increased in schizophrenia patients (SZ), but results have been equivocal. The current study investigates this phenomenon using a masked priming paradigm to isolate automatic effects. Differential automatic spreading of activation within the mental lexicon was examined using short and long stimulus onset asynchronies (SOA) between masked prime and target words. Short SOAs emphasize automatic processes, whereas long SOAs emphasize controlled processes.
Methods: Reaction times were recorded for 25 SZ and 29 healthy comparison (HC) subjects during a masked lexical decision task. Target words were preceded by masked primes that were either semantically related or unrelated to the target. Prime-target pairs were presented across short (190 ms) and long (910 ms) SOA conditions.
Results: HC subjects did not show significant priming in either SOA condition. SZ showed significant priming for words preceded by semantically related masked primes in the short SOA condition ($p<.05$). Greater automatic priming was associated with greater psychopathology (total SAPS $r=0.43$, $p<.05$, total PANSS score $r=0.49$, $p=.01$, PANSS positive $r=0.52$, $p<.01$, PANSS depression $r=.50$, $p=.01$, PANSS thought disturbance $r=0.48$, $p=.01$).
Conclusions: SZ show automatic semantic activation in a speeded task where

primes are not consciously perceived. The magnitude of this effect is related to clinical measures, suggesting that the automatic spread of activation within semantic memory is atypically increased in patients exhibiting greater symptom severity. This data supports the idea that greater automatic semantic activation is a major contributor to thought disorder.

278. Strategies for Enhancing Episodic Memory in Schizophrenia

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Background: Patients with schizophrenia may be impaired at relational memory (remembering relationships amongst items and the context in which they were encountered), even when memory for items is intact. This study investigated the impact of reducing relational demands by having patients encode pairs of items as a single unit (i.e., "unitization").
Methods: Preliminary data were obtained on nine patients and five controls who studied 280 noun pairs. Pairs were processed either as a single unit by requiring formation of a compound word ("unitized" trials) or as separate units by encoding them as part of a sentence ("non-unitized" trials). Participants were subsequently administered an associative recognition task including initial target pairs, and 280 recombined pairs. Receiver operator characteristics (ROC) were calculated to obtain estimates of recollection and familiarity.
Results: Unitization successfully increased familiarity-based retrieval, and this memory facilitation effect ($p<0.05$) was of similar magnitude for patients and controls. In contrast, recollection was not facilitated by the unitization procedure, and patients' recollection of unitized and non-unitized information remained close to zero.
Conclusions: This study provides preliminary evidence that patients may benefit from remediation strategies that encourage them to encode multiple items as a single combined representation to reduce relational memory demands and facilitate familiarity-based retrieval. Additional data will be obtained to confirm these preliminary findings, and future fMRI studies will investigate the hypothesis that patient deficits in hippocampal versus perirhinal function may account for this pattern of behavioral findings.
Supported by R01MH083734-01S1

279. Memory and Response Conflict in Schizophrenic Patients and Normal Controls

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Background: Interference from previous memory and response representations that conflict with current task performance must be resolved through cognitive control mechanisms. These mechanisms are deficient in schizophrenia.
Methods: Thirty-six schizophrenic patients and 35 controls were tested on an EEG short term memory task adapted from Nelson et al's (2003) fMRI study. Subjects were presented with a 4 letter memory set and after a short delay indicated whether a probe letter was in the memory set. One hundred-twenty probes were in the current memory set and 120 were not. Forty "negative" probes were in the previous memory set (memory conflict) and another 40 negative probes were not only in the previous memory set but were also the previous correct probe (memory and response conflict).
Results: Patients made more errors than controls, but did not show selectively increased errors on conflict trials. Patient error rates on conflict trials correlated with semantic and working memory WAIS III measures. Groups did not differ in a negative-going N2-like event-related potential (ERP), but patients showed a significantly smaller positive-going P3-like ERP. Furthermore, error rates in patients correlated with the N2-like ERP, whereas error rates in controls correlated with the later P3-like ERP.
Conclusions: In the face of working memory conflict schizophrenia patients may rely more on cursory evaluative processes (reflected in N2) whereas controls utilize more elaborate evaluative processes (reflected in P3). It remains to be determined whether specific ERP-activity on this task can be localized to cingulate gyrus (N2) and to dorsolateral cortex (P3).
Supported by NIMH RO1 58704

280. Performance Based Assessment of Functional Skills in Severe Mental Illness: Results of a Large-scale Study in China

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Background: Performance-based assessments of everyday living skills have been shown to be highly correlated with cognitive functioning in schizophrenia and bipolar disorder, as well as being predictive of deficits in real-world outcomes such as independent living and employment. Recent studies have suggested that impairments in these everyday living skills are quite consistent in people with schizophrenia who were assessed in the US and in Sweden, suggesting that these deficits may be a central feature of serious mental illness. In this study, we expand our assessments of impairments in everyday living skills to China, evaluating people with schizophrenia, bipolar disorder, and major depression, and comparing their performance to a large sample of healthy controls.
Methods: The UCSD performance-based assessment, brief version (UPSA-B), was translated and modified for use in Mandarin speakers in China. Samples of people with schizophrenia (N=272), bipolar disorder (n=61), major depression (n=50), and healthy controls (n=284) were examined with the Chinese version of the UPSA-B. Performance was compared across the groups and the association between educational attainment and UPSA-B scores was evaluated.
Results: The patients with schizophrenia had lower levels of education than the other three groups of subjects. When the performance on the UPSA was compared across the groups, with education as a covariate, significant effects of both diagnosis ($F=86.3$, $p<.001$) and education were found ($F=228.3$, $p<.001$). Post-hoc comparisons revealed that UPSA-B scores were lowest in the schizophrenia patients, followed by the patients with major depression. Patients with bipolar disorder did not differ from the healthy comparison subjects. Scores for all groups were lower than previously reported in western samples (e.g., HC mean = 64), but the highest educated subjects had scores consistent with those seen previously in US samples, for both schizophrenia patients (M=78) and healthy controls (M=83).
Conclusions: While diagnostic differences in UPSA-B scores are similar to those previously seen in western samples, the education effect is considerably more substantial. These data suggest that in developing countries educational attainment, which is often a proxy for urban residence, is strongly associated with levels of adaptive functioning and should inform clinical studies that are attempting to treat functional and cognitive deficits in multi-national contexts.
Supported by nimhu01mh079639

281. Dose-Response Effects of Single-Dose Modafinil on Cognition in Schizophrenia

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Background: Schizophrenia is characterized by deficits in a range of cognitive processes, which are modulated by central catecholamine systems. There is

also evidence for hypoactive catecholamine function in schizophrenia in the prefrontal cortex, which supports many of these cognitive processes. Therefore, pharmacologic agents which enhance dopamine and norepinephrine neurotransmission should have efficacy for these deficits. It remains unclear whether pro-catecholamine agents exhibit complex dose-response relationships, and which measures of cognition may be most sensitive to these pro-cognitive effects. We tested these problems with a dose-ranging study of modafinil, a combined norepinephrine/dopamine transport (NET/DAT) inhibitor, and compared measures from the MATRICS battery with those derived from a basic cognitive neuroscience theoretical framework.

Methods: 20 clinically-stable patients with schizophrenia or schizoaffective disorder (by DSM-IV-TR) performed a within-subjects test of single doses of 0, 100, 200 and 400 mg oral modafinil. Dose order was randomized and double-blind. Subjects performed the cognitive battery between 2-5 hours after dosing.

Results: To date, the patients show significant positive medication effects on performance on measures of working memory, episodic memory and cognitive control. These effects are in addition to practice effects, observed on most of the cognitive measures.

Conclusions: Enhancement of catecholamine neurotransmission with transport inhibitors has efficacy in single doses for the cognitive deficits of schizophrenia. Further work is needed to establish optimal dosing, including the relationship of single-dose to sustained treatment effects, the specificity of cognitive processes involved (including their neural basis), and the best measures (both cognitive and neuroimaging) to detect these effects.

Supported by NCRR

282. Chronic Methamphetamine Administration Causes Differential Regulation of Dopaminergic Transcription Factors in the Rat Ventral Midbrain

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Background: Methamphetamine (METH) is an illicit drug that can cause many neuropsychiatric complications. Challenges with large METH doses cause decreases in striatal dopamine (DA) concentration. However, repeated injections of small METH doses provide protection against METH-induced DA depletion. The protection might occur through regulation of developmental DA transcription factors.

Methods: Sprague-Dawley rats were injected with either saline or progressively increasing doses of METH over 2 weeks. Animals were then challenged with either saline or toxic doses of METH (5 mg/kg x 6 given one hour apart). Two weeks later, the animals were euthanized for measures of striatal DA levels. We also used quantitative PCR to measure mRNA levels for several transcription factors that participate in the differentiation and maintenance of mesencephalic DA neurons.

Results: METH pretreatment caused protection against METH-induced striatal DA depletion. Injections of toxic doses of METH caused significant decreases in the levels of *Nurr1* and sonic hedgehog (*Shh*) mRNAs but not in *Pitx3* expression. METH pretreatment followed by METH challenges was also associated with decreases in *Nurr1* but not in *Shh* expression. Finally, METH pretreatment caused significant increases in *Pitx3* expression after the toxic METH challenge.

Conclusions: Toxic doses of METH induce differential patterns of regulation of transcription factors that maintain ventral midbrain DA neurons. The METH-induced increase in *Pitx3* expression after METH preconditioning suggests that this transcription factor might play an important role in protecting nigrostriatal DA neurons against METH-induced injury.

Supported by NIH Intramural Research Program

283. Epigenetics of Fetal Alcohol Syndrome

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Background: Fetal alcohol exposure leads to the developmental changes of Fetal Alcohol Syndrome and Fetal Alcohol Spectrum Disorder. The molecular basis of FAS is unknown, but appears to involve both molecular and structural changes in the brain. Although several plausible molecular theories have been advanced to explain FAS (e.g. oxidative damage, acceleration of apoptosis, alterations in retinoic acid metabolism) there is no proven mechanism. For genome-wide assessment of alterations in chromatin structure and gene expression associated with FAS, we applied massively parallel sequencing to a neural progenitor cell model of alcohol exposure.

284. Translational Development of Novel Pharmacotherapeutic Strategies for Psychostimulant Dependence

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Background: Psychostimulant abuse generates profound socioeconomic, legal and medical problems worldwide, and is a significant comorbid factor that can adversely affect the clinical courses of other psychiatric disorders. Several agents, all employed as monotherapies, have failed to show consistent clinical efficacy against psychostimulant dependence. These failures highlight a critical, unmet medical need for the development of more robust treatment strategies. Based on recent advances in the learning and memory field, we have hypothesized that combinations of a psychostimulant or a non-abused "substitute" agonist with a 5-HT3, 5-HT2A/2C, or NK-1 antagonist may show enhanced efficacy in both animal models and human abusers.

Methods: Combinations of a "substitute" agonist (e.g., pergolide) and a selected receptor antagonist (e.g., ondansetron) have been tested in animal models. In a Phase II Clinical study, a combination of delayed-release ondansetron and immediate-release methylphenidate formulations is being tested utilizing multiple psychological assessment tools and neuroimaging.

Results: Preclinical data have demonstrated that the combined agonist/antagonist treatments can: (1) reverse consolidated behavioral sensitization; (2) attenuate cocaine self-administration under a progressive ratio paradigm; (3) attenuate cocaine or methamphetamine induced psychostimulant self-administration reinstatement; and (4) normalize associated neurobiological marker changes in selected brain regions. It is critical that the 5-HT3 antagonist ondansetron is given 3.5 hours after pergolide; furthermore, monotherapies using either agonists or antagonists alone are ineffective.

Conclusions: Combinations of a "psychostimulant substitute" and an antagonist at selected neurotransmitter receptors may hold therapeutic promise against psychostimulant dependence. Results from the current phase II study will help to translate preclinical findings into the clinical field and improve our understanding of the role of learning and memory mechanisms in stimulant dependence.

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285. The Role of Acetaldehyde in Human Psychomotor Function: A Double-Blind Placebo-Controlled Crossover Study

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Background: Acetaldehyde, the first product of ethanol metabolization, is a biologically active compound, but the behavioural properties of acetaldehyde in humans are largely undefined. We investigated the acute effects of both alcohol and acetaldehyde on psychomotor functions related to automobile driving skills.
Methods: Twenty-four men were selected through genotyping; half had the ALDH2*1/*1 (active form) genotype and half had the ALDH2*1/*2 (inactive form) genotype. In a double-blind placebo-controlled crossover design, each subject was administered one of the following doses of alcohol: 0.25 g/kg, 0.5 g/kg, 0.75 g/kg, or a placebo in four trials that took place at one-week intervals. Blood ethanol concentration (BEC) and blood acetaldehyde concentration (BAAC) were measured nine times and psychomotor function tests (critical flicker fusion threshold, choice reaction time, compensatory tracking task, and digit symbol substitution test) were assessed seven times in total over 4 hours after study drug ingestion.
Results: Following the consumption of alcohol, BEC was comparable in the two subject groups, while BAAC was significantly higher in subjects with ALDH2 *1/*2 than in those with ALDH2 *1/*1. The psychomotor performance of subjects with ALDH2*1/*2 was significantly poorer than that of subjects with ALDH2*1/*1. Significant correlations between psychomotor performance and both BEC and BAAC were observed. However, in the linear regression analysis, BAAC significantly predicted poorer psychomotor performance, whereas BEC was not associated with any measure of psychomotor function
Conclusions: Acetaldehyde may be more important than alcohol in determining the effects on human psychomotor function and skills.

286. Cognitive Functions and Affective Disorders in Chronic Hepatitis C Patients during Treatment with Interferon-Alpha plus Ribavirin

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Background: The aim of this prospective study was an assessment of affective disorders and cognitive functions in chronic hepatitis C (CHC) patients before and during interferon-alpha plus ribavirin (IFN+RBV) therapy.
Methods: Patients (aged 18-60 years) with compensated liver function and without significant neuropsychiatric adversities were assessed with the ICD-10 criteria for presence of affective disorders (ADs) on psychiatric examination together with cognitive testing before initiation and after 3 and 6 months of IFN+RBV therapy. Brief neuropsychological battery consisted of TMT and the Stroop Test. The tests results were z-transformed and compared to matched control group within age clusters (18-29; 30-39; 40-49 and 50-60 years).
Results: Overall, 183 CHC patients were assessed prior to the therapy, 141 of them completed the evaluation after 3 moths of the therapy and 131 of them were examined after 6 months of the therapy. At baseline, 38 patients had ADs, 51 were diagnosed with ADs at the second examination and 37 had ADs after 6 months of IFN+RBV therapy. The performance of CHC patients on all measures at three examinations was significantly worse than that of control group. Cognitive performance of CHC patients during IFN+RBV therapy was significantly better as compared to baseline. CHC patients with ADs did not change their performance as contrary to patients with no ADs who showed significant improvement on tasks involving psychomotor speed and working memory.
Conclusions: The latter points to the practice effects. Absence of this phenomenon in CHC patients with ADs during IFN+RBV therapy may indicate learning difficulties.

287. Cannabis Use Before Age 15 is Associated with Poorer Executive Functioning

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Background: Many studies have suggested that adolescence is a period of particular vulnerability to neurocognitive effects associated with substance abuse. However, few large sample studies have measured differences in cognitive performance between chronic cannabis users (CCU) who started in early adolescence (before age 15) with those who started later.
Methods: 104 CCU and 44 controls were evaluated with neuropsychological tasks, with focus on executive functioning. CCU were divided into two groups consisting of 49 early-onset (EO) users and 55 late-onset (LO) users. Comparisons involving neuropsychological measures were performed using GLM analysis of variance (ANOVA). The alpha level was set at $p < 0.05$ (two-tailed) for all analyses.
Results: EO showed significantly poorer performance compared to controls and LO on tasks assessing sustained attention, impulse control, and executive functioning.
Conclusions: EO CCU exhibited poorer cognitive performance than controls and LO in executive functioning. Chronic cannabis use, when started before age 15, may have more deleterious effects on neurocognitive functioning.

288. Memory Functioning in Abstinent Chronic Cannabis Users is Associated with Age of Onset and Years of Daily Consumption

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Background: Scientific evidence shows that verbal learning and memory abilities are the most consistently impaired cognitive functions in chronic cannabis users (CCU). The amount of cannabis consumed during life is directly correlated with poorer performance in memory. The main aim of the present study was to examine verbal episodic memory (VM) in abstinent CCU and to investigate correlation of cognitive deficits with long term and lifetime cannabis exposure.
Methods: Buschke's Selective Reminding Test (BSRT) was used to evaluate VM of 34 CCU compared with 40 healthy controls, matched by age, level of education, and IQ. Correlation between years of daily cannabis use and memory scores on BSRT was performed. CCU were abstinent for at least 7 days.

Results: CCU had poorer recall, required more reminders, and had lower long term retrieval and storage than controls. Each of these tasks was correlated with age of onset and increased years of daily cannabis use.
Conclusions: Cannabis use has deleterious effects on memory, even after a period of abstinence. The present study is consistent with several authors' conclusions that CCU exhibit poorer verbal memory than controls and that these deficits are associated with early onset and lifetime consumption.

289. Characteristics of College Freshmen who Abstain from Alcohol Consumption

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Background: Adolescent alcohol use studies report sample abstinence rates between 14% and 20% (Huang, 2008, Knight, 2003, Samson 1989). Most such research focuses on alcohol users, often listing alcohol abstinence as a study exclusion criterion. There is little evidence whether college students who abstain from drinking are significantly different from their non drinking peers in any other manner than drinking preference.
Methods: Subjects were a representative sample of college freshmen that included alcohol abstainers [N=127], social drinkers [N=163] and binge drinkers [N=384]. A sub sample of subjects also completed self-report measures of impulsivity. Alcohol abstainers were defined as subjects self-reporting a lifetime maximum consumption of zero alcohol-containing drinks in any 24-hour period. Binge drinkers were females who reported consuming >4 drinks (>5 drinks for males) in a drinking episode in the last 30 days. Social drinkers were classified as subjects who drank, but had not binged in the last 30 days. Groups were compared on computerized neuropsychological test and self-report measures derived from an anonymous website for multiple measures shown in Table 1.
Results:

Measure	Group	N	Mean	F value	p value
Perceived Social Support from Friends	Abstainer	127	34.9	4.91	0.00
	Social Drinker	163	37.06		
	Binge Drinker	384	37.85		
Perceived Social Support from Family	Abstainer	127	35.13	1.83	0.14
	Social Drinker	163	37.14		
	Binge Drinker	384	36.85		
Life Events Scale for Students	Abstainer	127	7.03	10.26	0.00
	Social Drinker	163	8.64		
	Binge Drinker	384	9.31		
Risky Family Assessment	Abstainer	127	26.1	0.43	0.74
	Social Drinker	163	26.8		
	Binge Drinker	384	25.87		
How much alcohol do you think is consumed by other college students of your gender	Abstainer	127	3.09	5.07	0.00
	Social Drinker	163	3.31		
	Binge Drinker	384	3.46		
Family History of Alcohol Use	Abstainer	110	0.3	2.19	0.11
	Social Drinker	159	0.47		
	Binge Drinker	364	0.4		
Sensation Seeking Scale: Thrill Seeking and adventure	Abstainer	43	6.09	6.05	0.003
	Social Drinker	83	5.9		
	Binge Drinker	185	7.06		
Sensation Seeking Scale: Disinhibition	Abstainer	43	3.21	43.40	0.000
	Social Drinker	83	4.25		
	Binge Drinker	185	6.31		
Baratt Impulsivity Scale-11: Attention	Abstainer	43	10.14	3.38	0.035
	Social Drinker	83	10.07		
	Binge Drinker	185	10.93		
Baratt Impulsivity Scale-11: Self Control	Abstainer	43	11.4	8.98	0.000
	Social Drinker	83	11.73		
	Binge Drinker	185	13.14		

Fig 1. Significant group differences were seen in impulsivity (SSS, BIS-11), perceived friend support, recent significant life events, and perceptions of alcohol consumption.
Conclusions: We found that our sample contained a higher level of abstinence (23 %) then generally reported in the literature. Additionally, while there were several significant between-group differences, these are mainly ascribable to differences in the binge drinker group and generally highlight similarities between social drinkers and abstainers.
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290. Dysfunctional Reward Processing in Current Cocaine Abusers during an Interpersonal Competitive Game

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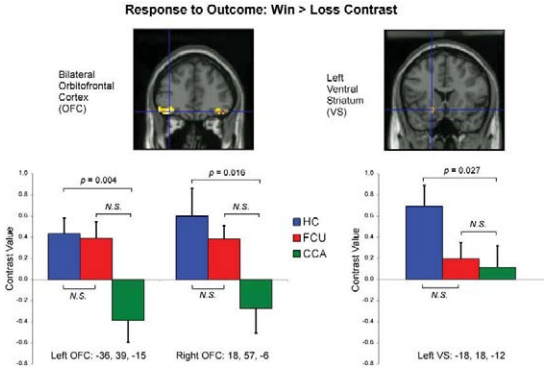
Background: Drug addiction is believed to depend on changes within the brain's reward circuitry. We investigated this circuit in the context of social interactions in current cocaine abusers (CCA) compared to former cocaine users (FCU) and healthy controls (HC). We hypothesized that during an interpersonal competitive game CCA will display dysfunctional social-reward neural activation, particularly in the ventral striatum (VS) and orbitofrontal cortex (OFC).
Methods: Twenty-one CCA, 19 FCU, and 21 HC performed a competitive Domino game fMRI task against what they believed was a human opponent. To win games, subjects were required to bluff their opponent on occasion, and thereby risk being caught and punished. We analyzed fMRI data from the Response to Outcome interval of the game, during which participants discovered whether they won or lost. Data were preprocessed and analyzed using SPM2 and SPSS software.
Results: During the Response to Outcome game interval, CCA showed reduced BOLD activation in several brain regions, including left VS and

bilateral OFC (p<0.05; uncorrected) when compared with HC and FCU.
Conclusions: Our results indicate that, during receipt of rewards in a socially competitive game, CCAs exhibit reduced activity in VS and OFC, key regions in the brain's reward circuit, when compared to HCs and FCUs. These results suggest dysfunctional neuronal social reward processing directly related to recent cocaine abuse.



Supported by RO1 AA015615

291. Validation of the Kreek-McHugh-Schluger-Kellogg (KMSK) Scale of Substance Use in an Urban Low-Income and Predominantly African-American Sample of Primary Care Patients

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Background: The Kreek-McHugh-Schluger-Kellogg (KMSK) scale was developed to quantify self-exposure to opiates, cocaine, alcohol, and tobacco. The orginal study was limited by a relatively small sample that was not representative of general clinical populations, and did not include marijuana exposure.
Methods: Participants were recruited from primary-care outpatient clinics in an urban public hospital. The primary measure was the KMSK scale. The Structured Interview for Diagnosis for DSM-IV (SCID) was used as the "gold standard" for substance dependence diagnoses, and the results of KMSK assessments were evaluated using Receiver Operator Characteristic (ROC) analysis.
Results: The sample (N=439) was predominantly African-American (90.6%), with mean age (± SD) of 43.1±12.8 yrs. ROC analyses found that the optimal cutoff scores for alcohol dependence were the same as suggested previously (11), while they were lower for cocaine dependence (10 vs 11) and opiate dependence (4 vs 9). The analysis suggested a cutoff score for marijuana of 8. Gender differences were observed in cutoff scores for cocaine and opiate dependence.
Conclusions: The KMSK performed well in the current study as a reliable and brief tool for evaluating dependence on alcohol, cocaine, marijuana and opiates in this nonpsychiatric clinic sample of predominantly poor urban African Americans.
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292. Functional Genetic Variants that Increase Synaptic Serotonin and 5-HT3 Receptor Sensitivity Additively Predict Alcohol and Drug Dependence

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Background: Serotonin (5-HT) has been implicated in addiction. The 5-HT transporter controls synaptic 5-HT availability. The 5-HT3 receptor mediates fast excitatory 5-HT transmission that modulates dopamine release in the reward circuitry. Functional polymorphisms in genes encoding the transporter and receptor may therefore influence addiction vulnerability.
Methods: African American men: 345 treatment seeking patients with lifetime DSM-IV diagnoses of alcohol, cocaine and heroin dependence and 172 controls, were genotyped for the triallelic 5-HTTLPR functional polymorphism in the transporter gene and the functional SNP rs1176744 Tyr129Ser in *HTR3B*, a gene encoding 5-HT3 receptors.
Results: The low activity 5-HTTLPR variant was more common in the total group of men with addiction compared with controls: p = 0.004, OR = 2.5 [1.5-4.3]. The *HTR3B* gain of function Tyr129Ser+Ser129Ser genotypes were likewise more common in men with any addiction: p = 0.016, OR = 1.5 [1.0-2.2]. The *5-HTTLPR* and *HTR3B* variants had an additive effect on any addiction (OR = 4.3 [1.9-9.6]). The strongest additive effects were seen in individuals with alcohol and drug dependence (OR = 6.0 [2.1-16.6]). Analyzed independently, the low activity 5-HTTLPR variant predicted cocaine dependence (p = 0.0009) and the *HTR3B* gain of function variant predicted alcohol dependence (p = 0.004).
Conclusions: Functional variants in the two genes had additive effects on addiction risk. It is possible that increased synaptic 5-HT plus increased 5-HT3 receptor responsiveness to 5-HT might result in enhanced dopamine transmission in the reward pathway that is associated with a greater risk for addiction.
Supported by NIAAA Intramural Research, NIDA RO1 DA 10336-02

293. Analyses of Association of the Serotonin Transporter Gene (Slc6a4) Variants with Alcohol Withdrawal Seizures (aws) and/or Delirium Tremens (dt)

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Background: An association of the long-short variation in the promoter of the *SLC6A4* gene (5-HTTLPR) with AWS and DT was found when compared to non-alcoholic controls (Sander et al 1997). A haplotype composed of the three loci in the *SLC6A4* gene (5-HTTLPR, intron 2 repeat and rs25531 SNP) has also been associated with remission of depressive symptoms following citalopram treatment (Mrazek et al. 2009). In this study we explored association of AWS and DT with these three variations in the *SLC6A4* gene.
Methods: Alcoholics with a history of withdrawal and presence (n = 112) or absence (n = 92) of AWS and/or DT were genotyped for three allelic variants in SLC6A4. Association of genotypes and haplotypes with the outcome was assessed using logistic regression.
Results: None of the genetic variants are individually significantly associated

with combined AWS/DT phenotype, seizures only, or DT only, except the promoter variant (5HTTLPR) which is associated with AWS/DT (p=0.008) but not when an additive allele effect is assumed (p=0.93). The number of LA haplotypes is associated with AWS/DT showing the same trend as the L allele, with the heterozygotes having a higher risk of AWS/DT. The haplotype analyses indicate a trend (not significant) that the LG haplotype is associated with lower odds of AWS/DT phenotype and with lower odds of AWS or DTs when considered as separate outcomes.

Conclusions: Our findings indicate a heterozygote disadvantage and thus do not provide a clear explanation for an association of the studied genetic variants with AWS and/or DT.

Supported by SC Johnson Genomics of Addiction Program

294. Oxytocin as a Novel Treatment for Drug Dependence: From the Bench, to the Street, to the Clinic

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Background: Increasing evidence suggests the neuropeptide oxytocin may be utilized as a treatment for a wide variety of psychopathologies, including addiction.

Methods: Firstly, we trained rats to lever press to intravenously self-administer methamphetamine. Once responding had stabilized, one group of rats received escalating doses of oxytocin prior to daily self-administration tests while other rats received vehicle. After these tests, lever pressing was extinguished and the ability of methamphetamine primes to reinstate responding was studied with and without co-administration of oxytocin. In a separate study, using Fos immunohistochemistry we determined the ability of oxytocin to compete with a methamphetamine challenge. To provide insight into alterations in neuropeptide systems during drug intoxication in humans we collected blood from a group of methamphetamine intoxicated adults and compared their plasma levels of oxytocin, vasopressin, and cortisol to a non-drug taking healthy control group.

Results: We showed that oxytocin dose-dependently reduced responding for intravenous methamphetamine in rats and significantly reduced relapse to drug-seeking. Secondly, our results showed that oxytocin effectively reduced methamphetamine induced neural activity in key addiction related brain areas as well as reduced methamphetamine induced hyperactivity to a level similar to that of control animals. Our data also provide further insight into the pharmacodynamic action of addictive substances, specifically methamphetamine in human drug users. Importantly, I will finish by discussing preliminary findings from a randomized controlled trial of intranasal oxytocin for cannabis dependence.

Conclusions: We provide important insight into the role of oxytocin in drug addiction and argue its use as a novel therapeutic for drug dependence.

295. Ethical Issues in Translational Research in Psychiatry

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Harvard Unviversity

Background: There is an explosion of neuroscientific investigation of animal models of psychiatric disorders. Research findings in animals raise scientific and ethical questions about how to translate this knowledge to humans and thereby improve research and treatment of psychiatric disorders.

Methods: A critical analysis of translational research in psychiatry is undertaken, and an ethical framework for this area is proposed.

Results: Translating research findings from animals to humans entails many challenges when the area of focus is psychiatric disorder. Human psychiatric disorders like depression comprise observable behaviors (e.g., psychomotor slowing, sleep disturbance, weight loss) and complex subjective experiences (e.g., despair, guilt, self-criticism). Since the former lend themselves more readily to modeling in animals than the latter, it is difficult to study crucial aspects of human depression in animals. Serious ethical precautions are needed when translating findings in animals to humans. Effective treatments for animals might not benefit humans, whose depressive experiences are marked by subjective experiences. Those treatments, therefore, might be too risky in clinical and investigational settings.

Conclusions: A pragmatic model for ethical translation of research findings in psychiatry is needed. The model must acknowledge difficulties of studying in animals the host of subjective experiences in human depression. The model must consider the risk/benefit profile of conducting in depressed humans clinical trials of treatments that are effective in animals. Disclosure of risks, rigorous informed consent process, and evaluation of competency are critical elements of an ethical clinical trial in this setting. Institutional review boards (IRBs) are well-positioned to attend to these challenges.

296. The Role of Arginine Vasopressin in Human Social Cognition

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Background: The structurally similar neurohypophyseal hormones arginine vasopressin (AVP) and oxytocin (OT) are intrinsically involved in social behavior. Although AVP is best-known as an anti-diuretic hormone, AVP receptors are widely distributed in the central nervous system. While OT is implicated in positive social interactions and facilitating approach behavior, AVP seems to be involved in specifically male behaviours, including inter-male aggression, scent marking, pair-bonds, and courtship, as well as learning and memory. Translational research between preclinical and human studies has also implicated AVP in the moderation of subjective, behavioural, and physiological stress responses.

Methods: Studies will be presented that employ randomized controlled trials of AVP nasal spray and a placebo nasal spray and assessing influence on tests of social cognition test.

Results: The results of these studies demonstrate that AVP nasal spray enhances the perception of social information. Contrasting influences between AVP and OT nasal spray will also be presented.

Conclusions: The influence of AVP on social cognition suggests a potential therapeutic role in the treatment of social problems. There are, however, differential effects of AVP and OT on social cognition tasks, and the implications for disorders with deficits in social cognition will be discussed.

297.-323. Late Breaking Posters

At time of publication the Late Breaking poster abstracts had not been accepted. Please see the on-line Program Planner at www.sobp.org for the complete abstracts accepted for this session.