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FRIDAY, MAY 21

PLENARY SESSION
Addiction
Friday, May 21, 2010 8:00 AM - 10:15 AM
Location: Grand Ballroom ABC
Chair: J. John Mann

324. The Genomics of Addiction
David Goldman
National Institute of Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, MD

Dr. Goldman received his B.S. from Yale University in 1974. He received his M.D. degree in 1978 and completed residency training in psychiatry in 1979, both at the University of Texas Medical Branch. Dr. Goldman joined the NIAAA in 1979 and has been Chief of the Laboratory of Neurogenetics since 1991. Throughout his career, Dr. Goldman has focused on the identification of genetic factors responsible for inherited differences in behavior, and he has authored over 300 papers. His laboratory is currently exploring the genetics of alcoholism and related psychiatric diseases, and is well-known for his work identifying effects of functional genetic variants on intermediate phenotypes for complex behavioral disorders.

325. Pharmacological and Genetic Modulation of Motivated Decision Making in Corticostriatal Circuits
Michael J. Frank
Brown University, Providence, RI

Michael J. Frank is Assistant Professor of Cognitive & Linguistic Science, Psychology, and Psychiatry in the Brown Institute for Brain Science at Brown University. He directs the Laboratory for Neural Computation. He received an undergraduate degree in Electrical Engineering at Queen’s University (Canada), followed by a Master’s degree in Engineering with biomedicine option at the University of Colorado at Boulder. He then received his Ph.D in Neuroscience and Psychology at the University of Colorado in 2004, followed by a year of postdoctoral work at the same institution. He then moved to the University of Arizona in 2006 until 2009 when he moved to Brown. Dr. Frank is an active member of multiple professional societies, including the Society for Neuroscience, the International Basal Ganglia Society, the Cognitive Neuroscience Society, and the Association for Psychological Science. He has authored over 40 publications, primarily on theoretical models of basal ganglia and dopamine function in cognition and their implication for Parkinson’s Disease and related disorders. This research utilizes computer models linking brain to behavior which are then tested and refined via experiments using pharmacological manipulation, deep brain stimulation, electroencephalography, and genetics. Awards include the DG Marquis award for best paper published in Behavioral Neuroscience (2006). Dr Frank is a Contributing Editor for the European Journal of Neuroscience, a member of Faculty of 1000 Biology (Theoretical Neuroscience section), Consulting Editor for the Journal of Mathematical Psychology, guest editor of a special issue of Cognition, and ad-hoc reviewer for over 30 professional journals across domains of neuroscience, cognitive science, psychology, and computational neuroscience. He has also served as an Ad Hoc grant reviewer for the National Science Foundation, the Wellcome Trust (UK), the Neurological Foundation of New Zealand, the Netherlands Organisation for Scientific Research, and the UK Economic and Social Research Council.

326. A Genomic Approach to the Treatment of Alcoholism
Charles P. O’Brien
Psychiatry, University of Pennsylvania, Philadelphia, PA

Charles P. O’Brien, a native of New Orleans, earned M.D. and Ph.D. degrees from Tulane University. He received residency training at Harvard, Tulane, University of London, and University of Pennsylvania in internal medicine, neurology and psychiatry and became board certified in both neurology and psychiatry. As Chief of Psychiatry at the Philadelphia VA Medical Center, he was responsible for over 9,000 psychiatric patients. Despite this large clinical responsibility, he was able to establish and direct a clinical research program that has had a major impact on the treatment of addictive disorders. His research group has been responsible for numerous discoveries described in over 500 publications that have elucidated basic information on the nature of addiction and improved the results of treatment for addictive disorders. His work involves discovery of CNS changes involved in relapse, new medications, behavioral treatments and instruments for measuring the severity of addictive disorders. He led the discovery of the effects of alcohol on the endogenous opioid system and demonstrated a completely new treatment for alcoholism. Many of his discoveries are now utilized in common practice for the treatment of addictive disorders throughout the world. His recent work has focused on a genetic subtype of alcoholism. A functional allele of the μ opiate receptor predicts response to alcohol and carries an increased risk of both alcoholism and opiate addiction. O’Brien was elected to the Institute of Medicine of the National Academy of Sciences in 1991 and he has received numerous research and teaching awards as well as an honorary doctorate from the University of Bordeaux in 1994 and the Nathan B. Eddy award for research on addiction from the College on Problems of Drug Dependence in 2003.

PRESIDENTIAL INVITED LECTURE
Addiction
Friday, May 21, 2010 10:50 AM - 11:50 AM
Location: Grand Ballroom ABC
Chair: J. John Mann

327. Addiction: Conflict Between Brain Circuits
Nora D. Volkow
National Institute on Drug Abuse, Bethesda, MD

Nora D. Volkow, M.D., became Director of the National Institute on Drug Abuse (NIDA) at the National Institutes of Health in May 2003. NIDA supports most of the world’s research on the health aspects of drug abuse and addiction. Dr. Volkow’s work has been instrumental in demonstrating that drug addiction is a disease of the human brain. As a research psychiatrist and scientist, Dr. Volkow pioneered the use of brain imaging to investigate the toxic effects of drugs and their addictive properties. Her studies have documented changes in the dopamine system affecting the actions of frontal brain regions involved with motivation, drive, and pleasure and the decline of brain dopamine function with age. She has also made important contributions to the neurobiology of obesity, ADHD, and the behavioral changes that occur with aging. Dr. Volkow was born in Mexico, attended the Modern American School, and earned her medical degree from the National University of Mexico in Mexico City, where she received the Premio Robins award for best medical student of her generation. Her

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329. PET Imaging of Methamphetamine Distribution and Kinetics in Humans

Joanna S. Fowler¹, Gene-Jack Wang², Nora D. Volkow³

¹Brookhaven National Laboratory, Upton, NY, ²Medical, Brookhaven National Laboratory, Upton, NY, ³National Institute on Drug Abuse, Bethesda, MD

Background: Methamphetamine (METH) is highly addictive producing produces larger and longer-lasting increases in brain dopamine (DA) than cocaine (COC) and is neurotoxic to DA cells. We measured the distribution and pharmacokinetics (PK) of METH in the human brain at tracer doses, comparing it with those of COC, and assessing the relationship between the PK of METH and its reinforcing effects.

Methods: PET and [11C]d-methamphetamine and [11C]cocaine were used to measure brain METH and COC. PK in 18 healthy men over 90 and 60 min respectively. METH PK in striatum was compared to the time course of the ‘high’ from a pharmacological dose of METH and to dopamine transporter (DAT) availability.

Results: METH distributed throughout the brain whereas COC concentrated in striatum. Peak striatal uptake was higher for COC than for METH and occurred earlier (4.5±1.1 vs 9.4±1.5 min). Clearance was slower for METH than for COC (64 vs 25% of peak C-11 remained at 90 and at 60 min respectively). METH PK in striatum paralleled the time course of the self-reported ‘high’ after pharmacological doses of METH (Newton et al., 2006). DAT availability correlated with METH uptake (R=0.6; p=0.007).

Conclusions: Widespread and long-lasting distribution of METH in the human brain may account for both its toxicity and the longer lasting behavioral effects relative to COC. Correlations between striatal METH and COC uptake suggest that a common variable governs the brain uptake to these two drugs. Funding: DOE-BER; NIH/NIDA; NIH/NIAAA; NIH/GCRC Supported by DOE-BER (infrastructure support); NIDA

330. Methamphetamine Self-Administration in Rats as a Model for Persistent Neuroadaptations in the Brains of Chronic Methamphetamine Abusers

Irina N. Krasnova

National Institute on Drug Abuse, NIH, DHHS

Background: Methamphetamine (METH) is an abused psychostimulant that causes damage to dopamine terminals in the brains of human addicts. Animal studies have also provided evidence for METH-induced neurotoxic effects to dopamine and serotonin terminals in rodent models. Because most rodent experiments involved multiple METH injections given in a single day, often referred to as an acute binge, there has been a discussion if this approach might represent human drug-taking behavior. Specifically, acute binge injections do not replicate increasing rate of METH intake by human addicts over time. Because METH self-administration is thought to better mimic human drug-taking behaviors, we examined if this pattern of drug administration results in damage to monoamine systems in the brain.

Methods: Rats were given access to METH for 15 hours per day for 8 days. Animals were euthanized at 24 hours, at 7 and 14 days after cessation of drug self-administration. Striata and cortices were dissected and frozen until used for HPLC and Western blot analyses.

Results: METH caused significant dose-dependent depletions in striatal dopamine concentrations throughout the period of observation. In addition, there were significant decreases in the dopamine transporter and tyrosine hydroxylase protein levels in the rat striatum. METH also caused significant depletion in cortical dopamine levels accompanied by reductions in the expression of dopamine transporter and tyrosine hydroxylase proteins at 14 days after cessation of drug intake.

Conclusions: These results suggest that METH self-administration can cause long-term neuroadaptations in the rat striatum and cortex in a fashion similar to effects reported in human chronic METH users.
331. Developing Pharmacotherapies for Methamphetamine Addiction

John E. Mendelson
California Pacific Medical Center Research Institute

Background: There are an estimated 11.7 million methamphetamine (MA) abusers in the United States and epidemics of MA addiction are occurring worldwide. In our human laboratory and outpatient clinical trials we use innovative methods to develop pharmacotherapies, quantify the severity and test biomarkers for MA addiction that may predict response to therapy or risk of relapse. One potential biomarker of addiction is the quantity of abused drug intake. Qualitative urinalysis is used in clinical trials and during treatment but provides only a binary outcome measure of MA abuse.

Methods: Using small, non-pharmacologic doses of deuterium labeled l-MA we have developed a continuous quantitative measure to estimate the bioavailable amount of MA addicts ingest during our treatment trials. The method has been validated in laboratory trials and will now be tested in upcoming outpatient trials. In a 60-subject outpatient trial we assessed the safety and efficacy of dextroamphetamine (d-AMP) as a substitution treatment for methamphetamine dependence. MA dependent outpatients were randomized to 30 mg sustained release oral d-AMP twice per day (N=30) or matched placebo (N=30). Adverse events and urine toxicology for methamphetamine were assessed twice per week for 8 weeks. Urine samples with <1,000 ng/mL of methamphetamine were classified as negative.

Results: There were no serious adverse events and d-AMP was well tolerated. Unfortunately, d-AMP did not decrease MA abuse.

Conclusions: The need for robust biomarkers of addiction and the implications of the failure of substitution therapy to suppress MA abuse will be discussed.

Supported by DA 018179.

Supported by DA 018179

332. Circuit-specific Alterations in the Strength, Kinetics and Nature of Cortical GABA Neurotransmission in Schizophrenia

David Lewis
UPMC, Pittsburgh, PA

Background: Impairments in cortical network oscillations, such as gamma frequency disturbances, might underlie the cognitive deficits in schizophrenia. Network oscillations depend, in part, on three physiological properties: 1) the strength [i.e., inhibitory post-synaptic current (IPSC) amplitude] of GABA neurotransmission as determined by both pre- and post-synaptic factors; 2) the kinetics (i.e., IPSC duration) of GABA neurotransmission as determined principally by the subunit composition of post-synaptic GABA-A receptors; and 3) the nature of the resulting inhibition (i.e., shunting or hyperpolarizing) as determined by Cl- ion flow when GABA-A receptors are activated. Each of these physiological features is dependent upon the expression of particular sets of gene products.

Methods: This presentation will present recent data indicating that alterations are present in each of these sets of gene products in the dorsolateral prefrontal cortex (DLPFC) of subjects with schizophrenia, and that at least some of these alterations occur in a circuit-specific fashion.

Results: In schizophrenia, 1) the well-established transcript deficit in GAD67 is accompanied by a deficiency in the cognate protein, supporting the idea that presynaptic GABA is reduced; 2) altered expression in specific GABA-A receptor subunits is likely to alter the speed of GABA neurotransmission at specific synapses; and 3) disease-related differences in the levels of kinases that regulate Cl- transporters may render GABA-A receptor activation less hyperpolarizing.

Conclusions: These findings suggest that the strength, kinetics and nature of GABA neurotransmission are altered in the DLPFC of subjects with schizophrenia, providing a molecular basis for the observed disturbances in cortical network oscillations.

Supported by NIH MH043784; MH084053

333. Genetic Regulation of GABA Activity and Risk for Schizophrenia


Genes, Cognition and Psychosis Program, NIH, NIMH, IRP, Bethesda, MD

Background: We have explored the association of genetic variation in GAD1 and risk for schizophrenia, related biologic intermediate phenotypes, interactions with other genes related to GABA neuronal activity, and GABA levels measured in vivo in human brain.

Methods: We identified distorted transmission of single-nucleotide polymorphism (SNP) alleles in two independent schizophrenia family-based samples (Straub et al., Mol Psych 2007). In both samples, allelic association was dependent on the gender of the affected offspring, and in the CBDB/NIMH sample it was also dependent on COMT Val158Met genotype.

Results: QTDT analyses revealed that variation in GAD1 influenced multiple domains of cognition, including declarative memory, attention and working memory. A 5’ flanking SNP affecting cognition in the families was also associated in unrelated healthy individuals with insufficient fMRl activation of dorsal prefrontal cortex (PFC) during a working memory task, a physiologic intermediate phenotype associated with risk for schizophrenia and altered cortical inhibition. A SNP in the 5’ untranslated (and predicted promoter) region that also influenced cognition was associated with decreased expression of GAD1 mRNA in the PFC of schizophrenic brain. We also observed evidence of statistical epistasis between the functional COMT Val158Met variant and SNPs in GAD1, suggesting a potential biological synergism leading to increased risk. This epistatic interaction was confirmed in normal subjects on fMRl measures of cortical inefficiency. We tested the effects of the six risk-associated SNPs in GAD1 and the COMT variant on GABA levels in the anterior cingulate cortex of 87 healthy volunteers measured with 3T magnetic resonance spectroscopy. There was a significant effect of genotype on GABA for three GAD1 SNPs and for COMT (all p<0.05). The risk associated GAD1 x COMT interaction was also significant (p<0.05). Surprisingly, risk alleles for schizophrenia in GAD1 were associated with higher GABA levels, and Val-Val homozygotes for COMT had higher GABA when on a GAD1 risk than on a non-risk genotype background.

Conclusions: These coincident results implicate GAD1 in the etiology of schizophrenia and suggest that the mechanism involves altered cortical GABA inhibitory activity, perhaps modulated by dopaminergic function.

*Supported by RO21MH70855-01A1

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*Supported by RO21MH70855-01A1
334. Functional Analysis of the Human GAD1 Promoter

Dennis R. Grayson
Psychiatry, University of Illinois Chicago, Chicago, IL

Background: Evidence is accumulating that in schizophrenia, cognitive deficits and appear to relate to a GABAergic neuronal pathology. The down-regulation of reelin and GAD67 mRNAs in post mortem brains with psychosis is well established. This is accompanied by an increased expression of DNA methyltransferase in these same neurons. We have previously reported that the reelin promoter is hypermethylated in cells not expressing the gene and that activation of expression with histone deacetylase (HDAC) inhibitors correlates with reduced methylation.

Methods: We have focused these studies on dissecting the human GAD1 promoter to better understand its regulation and whether methylation impacts expression. We have performed deletion analyses to examine proximal elements responsible for regulation. Our data indicate a region downstream of the transcription start site that is responsible for a large percentage of the promoter activity. This region is rich in CpGs and part of the GADI CpG island. We have used a combination of approaches to analyze promoter methylation and binding of repressor proteins after treating cells with chromatin remodeling drugs.

Results: Our results are consistent with the concept that the down-regulation of mRNAs in GABAergic neurons of schizophrenia brain may be the result of promoter hypermethylation. Drugs that inhibit HDACs activate the expression of reelin and GAD67. This appears to occur through a mechanism that involves the release of repressor proteins (Dnmts, MeCP2) from a complex promoter region.

Conclusions: Based on our findings it is reasonable that chromatin remodeling proteins may represent novel therapeutic targets for pharmacoeutical development.

335. Molecular Determinants of Dysregulated GABAergic Gene Expression in the Prefrontal Cortex of Subjects with Schizophrenia

Schahram Akbarian
University of Massachusetts Medical School, Worcester, MA

Background: Altered RNA expression, potentially affecting GABAergic neurotransmission and a wide range of other functions, is frequently observed in prefrontal cortex (PFC) and other regions of the schizophrenia postmortem brain. Therefore, the study of epigenetic determinants of neuronal gene expression may provide clues about the underlying molecular pathology.

Methods: Here, we explore epigenomes from the human PFC and study the distribution of various histone methylation markings at a subset of GABAergic genes at various stages of normal postnatal development, and in a case-control cohort for subjects with schizophrenia.

Results: Histone methylation is developmentally regulated at selected GABAergic genes, and cell-type specific (differentially regulated in NeuN+ neuronal and NeuN- nuclei from the same PFC tissue), and altered in some cases with schizophrenia, as reflected by shifts in open- and repressive chromatin-associated markings.

Conclusions: The “GABAergic epigenome” of the prefrontal cortex may provide important clues about the neurobiology of schizophrenia and related disease. Supported by NIH and IMHRO and NARSAD

336. Dopamine’s Role in ADHD Symptoms: Beyond an Attention Deficit

Nora D. Volkow1, Gene-Jack Wang2, Scott Kollins3, Tim Wigal4, Jeffrey Newcorn5, Frank Telang6, Joanna Fowler6, James Swanson4
1National Institute on Drug Abuse, Bethesda, MD, 2Brookhaven National Laboratory, Upton, NY, 3Duke University Medical Center, Durham, NC, 4University of California, Irvine, Irvine, CA, 5Mount Sinai Medical Center, New York, NY, 6National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD

Background: Attention Deficit Hyperactivity Disorder (ADHD) is characterized by deficits in attention and hyperactivity/impulsivity and there is increasing evidence that reward processing may also be disrupted in individuals with this disorder.

Methods: PET and [11C]clopride were used to measure dopamine D2/D3 receptor availability (predominant postsynaptic DA marker) and [11C]cocaine to measure dopamine transporter availability (presynaptic DA marker) in 53 adults with ADHD and 44 healthy controls.

Results: SPM data showed evidence of disrupted dopamine neurotransmission in nucleus accumbens (crucial brain region for motivation and reward) midbrain and caudate in never treated adults with ADHD. Moreover the decreases in DA markers were associated with symptoms of inattention, which highlights the importance of the dopamine brain reward circuitry in core symptoms of ADHD.

Conclusions: Inasmuch as the dopamine reward pathway is crucial for engaging attention we postulate that in some individuals with ADHD the primary deficit will not reside in attentional networks but in the DA circuits necessary to engage them. In this respect ADHD could be conceived not just as an “inattention deficit” disorder but in some instances as an “interest deficit” disorder. Clinical implications of these findings including the potential need for therapeutic interventions for ADHD that enhance the reinforcing and motivational responses to everyday tasks and the need for further investigation. Since dopamine brain reward pathways are also disrupted in addiction this presentation will also highlight the implication of these findings with respect to the increased vulnerability for substance use disorders in ADHD. Supported by NIAAA Intramural Research Program

*Supported by NIAAA
337. Anorexia Nervosa: Neural Circuit Bias towards Delayed Gratification, Inhibition, and Over-Concern with Consequences?

Walter H. Kaye1, Angela Wagner2, Amanda Bischoff-Grethe3, W Gordon Frankle4, Rajesh Narendran5, Guido G K Frank6, Vikas Duvvuri7, Ursula F. Baier5

1Psychiatry, University of California San Diego, La Jolla, CA, 2Child and Adolescent Psychiatry and Psychotherapy, J.W. Goethe University of Frankfurt, Frankfurt/Main, Germany, 3Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, PA, 4Radiology and Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, PA, 5Psychiatry, University of Colorado Denver, Aurora, CO, 6Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria

Background: How are individuals with anorexia nervosa (AN) able to starve and become emaciated when most people struggle to lose a few pounds? Imaging studies suggest exaggerated top-down neural processes can inhibit or override messages about inadequate energy consumption.

Methods: We used fMRI and PET to study individuals recovered (REC) from AN (normal nutrition and weight, regular menses) in order to avoid the confounding effects of malnutrition.

Results: Compared to matched controls, REC AN had 1) positive associations between the amount of dorsal striatum signal (in terms of fMRI response to positive and negative feedback), anxiety, and elevated DA D2/D3 receptor binding on PET. 2) Using amphetamine and PET/ raclopride, the magnitude of endogenous DA release in the dorsal striatum in REC AN was associated with anxiety, which is different than controls, where ventral striatum DA release is associated with euphoria. 3) REC AN showed preferential activation of dorsal circuitry, indicative of a preference for planning and consequences of choice, on a delayed discounting task designed to dissociate immediate vs. delayed gratification.

Conclusions: AN may have exaggerated function of dorsal neural circuits consistent with a bias for delayed is immediate gratification, and exaggerated inhibition, self-control, concern with consequences, and anxiety. Eating makes AN anxious, and starvation reduces anxiety. Palatable foods releases DA in the dorsal striatum and, in controls is thought to code the degree of pleasure from these foods. DA release is associated with euphoria. The ability of alcohol to stimulate human dopamine release may contribute to its rewarding effects and, thereby, to its abuse liability in humans.

338. Dopamine Release and D1 Binding in the Schizophrenia Spectrum

Larry J. Siever1, Judy Thompson2, Mark Slifstein2, Elisabeth Iskander1, Anissa Abi-Dargham2

1Mount Sinai School of Medicine, New York, NY, 2Columbia University, New York, NY

Background: The schizophrenia spectrum including chronic schizophrenia and schizotypal personality disorder (SPD) are characterized by deficient reward mechanisms or anhedonia. While the positive psychotic symptoms of the spectrum are more prominent in chronic schizophrenia, patients with SPD are more characterized by deficit symptoms, cognitive impairment, and anhedonia. Since dopamine has been implicated in reward, salience, and motivation, dopaminergic abnormalities may particularly underlie the reward as well as the cognitive deficits of the schizophrenia spectrum.

Methods: In this study, 16 SPD patients and 14 healthy controls were studied using a raclopride displacement paradigm following amphetamine administration to measure dopamine release and 19 SPD patients were studied in a D1 binding paradigm using [11C] NNC112 binding in comparison to 16 healthy controls.

Results: D1 binding in cortex was associated with executive function and working memory (p<0.05) while D, binding in striatum was associated with anhedonia (p<0.05). Regional D, binding alterations were different in pattern from those observed in schizophrenia. Dopamine release in striatum as measured by raclopride displacement was greater in schizophrenic patients than controls (p<0.05) with SPD patients intermediate between these two cohorts in data from a subset of these patients analyzed to date to be updated in the full cohort.

Conclusions: Abnormalities in reward circuitry as well as cognitive processes in the schizophrenia spectrum may be in part related to altered dopaminergic activity.

Supported by Veterans Affairs Merit Review Grant (7609-028); Mt Sinai GCRC - M01-RR-00071 from the National Center for Research Resources (NCRR)

339. Sex Differences in Alcohol Induced Dopamine Release in Young Adults: A PET Imaging Study

Anissa Abi-Dargham1, Nina Urban1, Mark Slifstein1, Larry Kegeles1, Xiaoyan Xu1, Diana Martinez1, Stephanie O’Malley2, John Krystal2

1Columbia University / NYSPI, New York, NY, 2Yale University, New Haven, CT

Background: Microdialysis studies in rodents have shown that alcohol administration stimulates dopamine release within the striatum. In order to understand the effects of alcohol on dopamine release in the human brain, we used a Positron Emission Tomography (PET) imaging paradigm with the D2/3 radiotracer [11C]raclopride to assess dopamine release induced by alcohol consumption in young social drinkers.

Methods: Young social drinkers (n=21) completed two PET scans with [11C] raclopride to derive the equilibrium partition coefficient of specifically bound to non-displaceable tracer, BPND. Before the scans, subjects received a juice mix containing ethanol, or trace ethanol. The percent difference in BPND (ΔBPND) was calculated. Blood alcohol levels were also obtained.

Results: Alcohol administration significantly displaced [11C] raclopride in all striatal subregions indicative of dopamine release, with the largest effect observed in the ventral striatum. Men had significant dopamine release in all subregions. In women, the change was restricted to the ventral striatum and precommissural putamen. Linear mixed model analysis across all striatal subregions with regional ΔBPND as repeated measure showed a highly significant effect of sex (p < 0.001).

Conclusions: This study provides definitive evidence that alcohol induces dopamine release in non-alcoholic human subjects, controlling for the associative impact of alcohol’s smell and taste. Further, alcohol produced greater dopamine release in men than women and greater subjective activation, despite similar blood alcohol levels. The ability of alcohol to stimulate human dopamine release may contribute to its rewarding effects and, thereby, to its abuse liability in humans.

Supported by NIAAA

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SYMPOSIUM
Toward Individualized Treatment for Depression: From Neurophysiology to Clinical Practice
Friday, May 21, 2010 12:30 PM - 2:30 PM
Location: Maurepas - 3rd Floor
Chair: Gerard E. Bruder∗
Co-Chair: Jonathan W. Stewart

*Supported by NIMH

340. Assessment of Monoamine Transmission in Animals to Identify Superior Antidepressant Strategies
Pierre Blier
Psychiatry and Cellular & Molecular Medicine, University of Ottawa, Ottawa, ON, Canada

Background: All antidepressant treatments thus far tested enhance serotonin (5-HT) transmission, albeit via different mechanisms. In so doing, some may also interfere with the activity of the norepinephrine (NE) or dopamine (DA) systems. It was thus postulated that by enhancing 5-HT transmission via more than one mechanism, a greater antidepressant response could be obtained. In addition, simultaneously targeting more than one of these systems should also lead to a superior antidepressant response.

Methods: Following repeated or sustained administration of antidepressants, electrophysiological recordings of 5-HT, NE, and DA neurons were obtained from anesthetized rats. Overall synaptic transmission was assessed by electrically stimulating the 5-HT or NE pathway, and/or by determining the degree of tonic activation of post synaptic neurons using selective antagonists.

Results: Selective serotonin reuptake inhibitors (SSRI), tricyclics, ECS, MAOI, bupropion, and mirtazapine enhanced 5-HT transmission. Greater increases were obtained by adding mirtazapine to a SSRI, by combining bupropion with a SSRI, and by adding the atypical antipsychotic aripiprazole to a SSRI. These strategies have all produced increased antidepressant action in the clinic.

Conclusions: Antidepressant strategies that optimize monoaminergic neurotransmission in the rat, as assessed electrophysiologically in vivo, appear to lead to superior antidepressant effects. Currently, the combination of a SSRI with bupropion from treatment initiation is being studied under double-blind conditions to determine if it will produce a more rapid and robust antidepressant action. Supported by Lundbeck, Schering-Plow, Bristol Myers Squibb, Canadian Institutes for Health Research, IRO1MH077285-01A2

341. Auditory Evoked Potential (AEP) and EEG Measures in Depressed Patients Predict Response to Antidepressants
Craig E. Tenke1,2, Jürgen Kayser1,2, Nathan A. Gates3, Daniel M. Alschuler4, Christopher J. Kroppmann5, Shiva Fekri6, Carlyle G. Manna7, Jonathan W. Stewart2,3, Patrick J. McGrath2,3, Gerard E. Bruder1,2

1Division of Cognitive Neuroscience, New York State Psychiatric Institute, New York, NY, 2Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, 3Depression Evaluation Service, New York State Psychiatric Institute, New York, NY

Background: Loudness dependency of auditory evoked potentials (LDAEP) is a functional measure that shows promise as a predictor of clinical response in depressed patients treated with serotonin agonists, and may complement tonic measures provided by resting EEG. A description of neuronal generator patterns underlying both measures is provided by principal components analysis of current source density waveform (CSD-PCA), which is a reference- and model-independent method recently developed in our laboratory. New findings using this approach will be presented for two studies.

Methods: Resting EEG (67-channels) was recorded from 54 unmedicated depressed patients before treatment with an SSRI or dual therapy (i.e., SSRI-bupropion or dual-mode antidepressant). In an ongoing AEP study (72-channels), LDAEP was measured in 15 depressed and 23 healthy adults who listened to binaural tones (1000 Hz; 40 ms; 1600-2100 ms ISI) at five intensities (60-100 dB SPL). Subsequently, patients were randomly assigned to treatment with an SSRI, bupropion, or both antidepressants.

Results: A distinctive low-alpha/theta EEG factor had a lateral-posterior topography with a secondary midline distribution. Treatment responders (n=36) showed significantly greater low alpha/theta activity compared to nonresponders (n=18). For LDAEP, an N1 factor with a tangentially-oriented topography, consistent with activation of auditory cortex, showed a robust, monotonic association with intensity, and was significantly greater for treatment remitters (n=7) than nonremitters (n=8), who did not differ from controls. A P2 factor (vertex source) showed a nonsignificant trend for a predicted difference in loudness dependency between remitters and nonremitters.

Conclusions: CSD-PCA measures characterized functional and tonic differences in neuronal activity related to treatment response. Supported by MH036295; MH066597

342. Quantitative EEG Measures of Frontal Activity as Biomarkers for Predicting Treatment Outcomes in Major Depression
Ian A. Cook
UCLA Semel Institute for Neuroscience & Human Behavior, UCLA Depression Research & Clinic Program, Los Angeles, CA

Background: While patients with major depressive disorder (MDD) commonly experience a delay between starting antidepressant treatment and symptom improvement, neurophysiologic changes may emerge in the first week of treatment. Replicated findings relating early quantitative EEG (QEEG) changes to later outcomes support the use of QEEG as a predictive biomarker. We will review data from two trials that highlight a focus on changes in frontal regions.

Methods: In the first study, a midline and right-frontal (MRF) region of interest, previously identified in healthy adults exposed to antidepressants, was examined in 72 adults with MDD from placebo-controlled antidepressant trials (fluoxetine, venlafaxine). Changes in QEEG cordance were calculated, comparing pre-treatment baseline to 48 hours, 1- and 2 weeks of treatment. In the second study (BRITE-MD), 375 adults with MDD enrolled in a trial with randomization to treatment (escitalopram ESC, bupropion BUP, or the combination COMB) after a week of exposure to ESC. QEEG was recorded with a frontally-focused montage at baseline and 1 week visits, yielding the ‘Antidepressant Treatment Response’ (ATR) index as a composite of alpha and theta features.

Results: In the first study, decreases at 1 week in theta-band MRF cordance values predicted 8-week remission with 90% sensitivity and 60% specificity (69% accuracy), and were unrelated to placebo outcomes. In BRITE-MD, ATR predicted ESC remission with 61% sensitivity, 82% specificity (74% accuracy). ATR predicted ESC remission with 61% sensitivity, 82% specificity (74% accuracy). ATR predicted ESC remission with 61% sensitivity, 82% specificity (74% accuracy).

Conclusions: Early frontal physiologic changes can predict clinical treatment outcomes in MDD. Refinements and replications (PRISE-MD and BOLD trials) will bring this biomarker approach closer to clinical application. Supported by R01MH069217, R01MH085925, RC1MH088438, Aspect Medical Systems,
343. Initial Exploration of an fMRI-Based Algorithm for Selecting Patients into Treatment with Cognitive Behavior Therapy (CBT) and Antidepressants

Greg J. Siegle1, Edward S. Friedman1, Michael E. Thase2
1Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA; 2Department of Psychiatry, University of Pennsylvania School of Medicine, Pittsburgh, PA

Background: We are working to personalize treatment for unipolar depression via pre-treatment fMRI. Literature suggests that CBT increases prefrontal control yielding decreased limbic reactivity whereas SSRI’s target limbic reactivity more directly. Thus, we hypothesized that limbic activity would predict response to both CBT and SSRIs whereas decreased activity in regions associated with executive control would predict response to CBT and not SSRI’s.

Methods: We will present a formal review of neuroimaging treatment studies of SSRI and CBT response and 2) initial data from three preference cohorts of CBT and SSRI for recurrent depression in which pre-treatment fMRI of emotional information processing was assessed on three scanners (total n=53).

Results: Published data suggest that response to CBT and SSRI’s is associated with pre-treatment amygdala activity; response to SSRI is associated with increased rostral cingulate activity whereas response to CBT is associated with decreased rostral/subgenual cingulate activity. At our sites, using a threshold of clinical significance of explaining >40% of the variation in residual symptomatology, increased amygdala activity predicted response to treatment (2/3 scanners), and decreased subgenual cingulate activity predicted response to SSRI (3/3 scanners). In contrast to the literature, in our limited sample (n=6), decreased rostral cingulate activity predicted increased response to CBT; DLPFC activity differentially predicted response to CBT and SSRI.

Conclusions: Initial data from both the literature and multiple cohorts at our site are initially supportive of algorithms that could be used to predict response to treatment and potentially differential response across CBT and SSRI treatments.

Supported by MH074807; MH082998; MH58397; Pittsburgh Foundation

344. Physiological, Neurochemical and Behavioral Analyses of the Neuregulin Signaling Pathway in Wild-Type and Mutant Mice: Implications for Schizophrenia

Andres Buonanno
NICDH, NIH

Background: Genes encoding Neuregulin-1 (NRG-1), and its receptor ErbB4, are genetically associated with schizophrenia. We have investigated how NRG-ErbB signaling influences synaptic and cognitive functions thought to be affected in schizophrenia, such as glutamatergic and dopaminergic synaptic transmission and plasticity, and neuronal network activity associated with working memory (i.e. gamma oscillations).

Methods: We used neurochemical, immunohistochemical, electrophysiological and behavioral approaches to investigate how NRG-ErbB signaling reverses LTP and regulates gamma frequency oscillations in the hippocampus of wild-type and mutant mice.

Results: We found that NRG-1 rapidly and dramatically stimulates hippocampal dopamine release, and that subsequent activation of D4 receptors (D4Rs) reverses LTP by promoting AMPAR internalization. The depotentiation effects of NRG-1, D4R agonist and theta pulse stimuli on LTP are blocked by several D4R antagonists (including clozapine), and are absent in D4R knockout mice. NRG-1 also enhances by approximately 20-fold the power, but not frequency, of kainate-induced gamma oscillations in acute hippocampal slices. Consistent with these observations, ErbB4 in the cortex is restricted to GABAergic interneurons including parvalbumin-positive basket cells that regulate gamma oscillatory power, and accumulates at glutamatergic postsynaptic sites. Mice harboring mutations in distinct components of the NRG-1 signaling pathway manifest behavioral deficits, as well as altered hippocampal synaptic plasticity and gamma oscillatory activity.

Conclusions: The effects of NRG-1 on dopamine and glutamate neurotransmission/plasticity and gamma oscillatory power, and the selective expression of ErbB4 in GABAergic interneurons, could have important implications for understanding how imbalances in NRG-ErbB signaling contribute to the pathophysiology associated with schizophrenia.

Supported by Eunice Kennedy Shriver National Institutes of Child Health and Human Development, NIH Intramural Research Program

345. Neuregulin Signaling in Cortico-Limbic Circuits Compromised in Schizophrenia

Lorna W. Role
SUNY Stony Brook, New York, NY

Background: Nrg 1 is a schizophrenia susceptibility gene. Post mortem analysis revealed altered ratios of Nrg1 isoform expression; including increased Ig isoforms and decreased expression of Type III Nrg1. The relative balance of expression of these isoforms is likely to play a critical role in mediating Ngl’s effects on the development, maintenance and plasticity of circuits that are compromised in Schizophrenia.

Methods: To test whether imbalance in neuregulin1 signaling contributes to altered cortico limbic behaviors we have examined gene dosage effects of Type III Nrg1 isoforms on the function of circuits underlying sensory gating and short term memory using in vivo multisite electrode recording and slice electrophysiology

Results: Type III Nrg1 heterozygous mice have severely disrupted prepulse inhibition and their performance in an alternating T maze task degrades as a function of memory load. In vivo recording of ventral hippocampal-nucleus accumbens circuits reveals disruption in phase locking of activity and disruption of temporal coherence consistent with altered fidelity of the cortico-limbic circuits. Slice recording reveals disruption in plasticity of cortico-limbic circuits with shift in threshold for LTP and for the nicotine induced shift in threshold of STP to LTP.

Conclusions: The selective disruption of even one of the many classes of Nrg1 isoforms is sufficient to cause significant alterations in cortico-limbic behaviors and circuits. We propose that it is the relative balance of signaling via multiple Nrg1 isoforms that is essential to the formation and maintenance of proper synaptic connections and to the plasticity of cortical -limbic circuits.

Supported by NARSAD and McKnight Foundation

*Supported by Wellcome Trust

SYMPOSIUM

Mouse Models of Neuregulin Signalling and their Relevance to Schizophrenia

Friday, May 21, 2010 12:30 PM - 2:30 PM
Location: Grand Chenier - 5th Floor
Chair: Amanda J. Law
Co-Chair: Paul J. Harrison*

*Supported by Wellcome Trust
346. TM-Domain Neuregulin-1 Mutants: Ethological, Social, Cognitive and Neurological Phenotypes in Relation to Schizophrenia
John L. Waddington, Colm M. P. O'Tuathaigh
Molecular & Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland

**Background:** Among several candidates, neuregulin-1 (NRG1) endures as a putative susceptibility gene for psychotic illness. Given the involvement of NRG1 in numerous aspects of brain development and synaptic function, phenotypic studies in NRG1 mutants can inform on the functional roles of this gene vis-à-vis schizophrenia and related psychoses. Here we describe phenotypic studies on transmembrane (TM)-domain mutants with heterozygous deletion of NRG1.

**Methods:** The ethogram, i.e. resolution and quantification of all individual topographies of behaviour in the mouse repertoire to define how they change and intertace over time to reveal basic processes of environmental interaction and adaptation. Social behaviour, in terms of sociability, social novelty reference and dyadic social interaction. Cognition, in terms of spatial learning and working memory. Neurological function, in relation to the long-standing debate on the extent to which schizophrenia is associated with movement disorder, particularly orofacial dyskinesia, even in the absence of treatment with antipsychotic drugs.

**Results:** Our findings indicate TM-domain NRG1 mutants to evidence disruption to the ethogram, to social novelty preference and dyadic social interaction, in the absence of major effects on spatial earning and working memory, together with abnormalities of orofacial function.

**Conclusions:** While these data inform on the functional role of NRG1 in the context of its association with risk for schizophrenia, possible gene × gene interaction, in the absence of major effects on spatial earning and working memory. Neurological function, in relation to the long-standing debate on the extent to which schizophrenia is associated with movement disorder, particularly orofacial dyskinesia, even in the absence of treatment with antipsychotic drugs.

347. The Hippocampal Phenotype of Transgenic Neuregulin 1 Type I Over-Expressing Mice
Paul J. Harrison
Psychiatry, University of Oxford, Oxford, United Kingdom

**Background:** There is increased expression of the type I isoform of neuregulin 1 (NRG1) in the cerebral cortex in schizophrenia. Virtually nothing is known about the interactions of NRG1 type I in the brain, and so the significance of this over-expression is unclear. We have investigated this issue using a mouse that selectively over-expresses NRG1 type I (NRG1<sup>100S</sup>.)

**Methods:** NRG1<sup>100S</sup> +/+ mice were compared to their wildtype (wt) littermates on a range of behaviours. We also measured synaptic transmission, long-term potentiation (LTP) and other electrophysiological indices; hippocampal gene expression using microarrays, and hippocampal morphometry and immunocytochemistry.

**Results:** NRG1<sup>100S</sup> +/+ mice showed an age-emergent impairment of spatial working but not reference memory. Basal hippocampal synaptic transmission and LTP were normal, but the NRG1<sup>100S</sup> +/+ mice did have other electrophysiological abnormalities. Expression of many transcripts was altered, notably affecting immune/inflammatory genes. The hippocampus of NRG1<sup>100S</sup> +/+ mice was selectively enlarged and showed subtle cytoarchitectural differences.

**Conclusions:** NRG1<sup>100S</sup> +/+ mice have a complex phenotype affecting all domains measured. The data indicate that the type I isoform of NRG1 contributes to hippocampal function and dysfunction. Some but not all of the alterations consistent with findings in other genetic mouse models of schizophrenia.

Supported by Wellcome Trust

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anterior thalamus and cingulate, compared to controls. Reductions in BPND were also observed in FMS in partly overlapping areas: nucleus accumbens, amygdala and anterior cingulate, correlating with clinical pain and depression ratings. BPD was however characterized by increases in BPND in the cingulate, caudate, accumbens and amygdala, and reductions in the thalamus, correlating with dissociative symptom scores in the basal ganglia.

Conclusions: These data demonstrate a substantial overlap between neurochemical systems and brain regions involved in the regulation of mood, affective state and pain, with characteristic alterations in pathological states involving those processes.

Supported by R01 DA 023520, R21 MH 069612, Prizker Foundation.

350. Altered Functional Brain Response during Anticipation and Processing of Heat Pain in Major Depressive Disorder (MDD)

Irina A. Strigo
University of California San Diego

Background: Chronic pain and depression are highly comorbid conditions, yet little is known about the neurobiological basis of pain processing in major depressive disorder (MDD). This study examined neural substrates underlying anticipation and processing of heat pain in MDD.

Methods: Fifteen unmedicated MDD and 15 healthy subjects underwent functional magnetic resonance neuroimaging (fMRI). Painful and non-painful heat stimuli were applied while different color shapes signaled the intensity of the upcoming stimulus.

Results: MDD compared to healthy controls showed: (1) increased activation in right frontoinsula, dorsal anterior cingulate and right amygdala during anticipation of painful relative to non-painful stimuli, (2) increased activation in right amygdala and decreased activation in periaqueductal gray, rostral anterior cingulate and prefrontal cortices during painful stimulation relative to non-painful stimulation, and (3) in MDD subjects greater activation in the right amygdala during anticipation of pain was associated with greater levels of perceived helplessness.

Conclusions: These findings suggest that increased emotional reactivity during the anticipation of heat pain may lead to an impaired ability to modulate pain experience in MDD. Future studies should examine the degree to which altered functional brain response during anticipatory processing affects ability to modulate negative affective states in MDD, which is a core characteristic of this disorder.

Supported by BNI, MH080003, MH077205, NARSAD

351. The Influence of Mood Induction on Pain Perception in Helathy Subjects and Controls

Karl J. Bär
Friedrich Schiller University Jena, Jena, Germany

Background: The complex sensory experience of pain involves cognitive, behavioural and emotional aspects which are closely interrelated. While patients suffering from major depressive disorder (MDD) mainly exhibit increased thresholds towards experimentally induced thermal pain applied to the skin, the induction of sad mood increases pain perception in healthy controls.

Methods: The presentation will focus on the neurobiological underpinnings of the discrepancy of pain perception in depression and after sad mood induction in healthy volunteers. Pain threshold data will be shown on changes of pain perception after sad mood induction in MDD and controls by means of fMRI. Patients and controls were rated on mood scales and results will be correlated to brain activity.

Results: We found a highly significant reduction in heat pain threshold on the left hand. Subjects were scanned twice, one group before and after sad-mood induction and another group before and after neutral-mood induction, respectively. Our main finding was a significant groupxemotion induction interaction bilaterally in the ventrolateral nucleus of the thalamus indicating a BOLD signal increase after sad-mood induction and a BOLD signal decrease in the control group.

Conclusions: We present evidence that induced sad affect leads to reduced heat pain thresholds in healthy subjects. This is probably due to altered lateral thalamic activity, which is potentially associated with changed attentional processes. Furthermore we present evidence for similar changes in depressed patients after sad mood induction.

**Supported by 5RO1MH076971-01**
**Supported by NIMH RO1MH068376; NCCAM 1R21AT002974**

352. Major Depression and Variation in TREK1 Gene Are Associated with Blunted Striatal Responses to Rewards

Diego A. Pizzagalli1, Avram J. Holmes1, Daniel G. Dillon1, Ryan Bogdan1, Sunny J. Dutra1, Roy H. Perlis2, Maurizio Fava3

1Harvard University, Cambridge, MA, 2Massachusetts General Hospital, Boston, MA

Background: Anhedonia (lack of reactivity to pleasurable stimuli) is a cardinal symptom of major depressive disorder (MDD) and has been associated with increased vulnerability to psychopathology and poor treatment outcome across disorders. Despite this evidence, the neurobiological underpinnings of anhedonia remain poorly understood in humans. In two studies, we tested the hypothesis that MDD participants and psychiatrically healthy individuals carrying genetic variants linked to poor antidepressant response would show reduced reward-related responses in basal ganglia regions.

Methods: In both studies, functional magnetic resonance imaging (fMRI) was used in conjunction with a monetary incentive delay task that dissociates anticipatory and consummatory phases of reward processing.

Results: In Study 1, relative to healthy controls (n=31), MDD participants (n=26) showed significantly weaker responses to gains in the left nucleus accumbens and bilateral caudate. In Study 2, we genotyped an independent sample of healthy participants (n=31) for the TREK1 gene. TREK1 is a two-pore-domain background potassium channel involved in regulating the excitability and resting potential of neurons; of note, TREK1 knockout mice display a depression-resistant phenotype (Heurteaux et al., 2006) and TREK1 genetic variants have been linked to antidepressant response in humans (Perlis et al., 2008). Critically, individuals carrying variants linked to positive antidepressant response showed potentiated basal ganglia responses to gains (but not penalties or no change feedback).

Conclusions: Collectively, these findings indicate that MDD subjects and healthy individuals at increased genetic risk for depression are characterized by blunted responsiveness in mesolimbic pathways implicated in hedonic coding and reinforcement learning.

Supported by NIMH RO1MH068376; NCCAM 1R21AT002974

**Supported by NIMH RO1MH068376; NCCAM 1R21AT002974**
353. Diminished Dopamine Release in Response to Unpredicted Monetary Reward in Major Depressive Disorder
Wayne C. Drevets¹, Chantal Martin-Soelch²
¹NIMH, ²Psychiatry, University Hospital Zurich, Zurich, Switzerland

Background: Corticolimbic networks that modulate the neural processing of reward and behavioral incentive are implicated in the pathophysiology of major depressive disorder (MDD) by data from neuroimaging and neuropathological studies. We investigated whether dopamine release in the ventral striatum differs between depressed subjects and healthy controls in response to unpredicted monetary reward.

Methods: Differences in the regional D2/3 receptor binding potential (ΔBP) between an unpredictable reward condition and a sensorimotor control condition were measured using the bolus-plus-constant-infusion [C-11]raclopride method. During the reward condition subjects randomly received monetary awards while performing a “slot-machine” task.

Results: While receiving unpredictable rewards the healthy controls showed a significant decrement in [C-11]raclopride binding in the reward condition versus the sensorimotor control condition in the right ventral striatum, presumably reflecting increased dopamine release. In contrast, the MDD subjects did not show any significant change in [C-11]raclopride binding during reward in the anteroventral striatum, and the mean ΔBP was significantly less in the depressed subjects than in the healthy controls.

Conclusions: Depressed patients showed abnormally reduced dopamine release during reward processing. These data converge with evidence from preclinical studies to support circuitry-based models that may elucidate the neural basis of anhedonia and amotivation in MDD. Such models also may form a basis during reward processing. These data converge with evidence from preclinical studies to support circuitry-based models that may elucidate the neural basis of anhedonia and amotivation in MDD. Such models also may form a basis during reward processing.

354. Reward Function in Adolescent Depression: Brain, Behavior, Mood, and Treatment Response
Erika E. Forbes¹, Ahmad R. Hariri², Neal D. Ryan³, Boris Birmaher¹, David A. Axelson¹, Ronald E. Dahl¹
¹Western Psychiatric Institute and Clinic, University of Pittsburgh, Pittsburgh, PA, ²Psychology, Duke University, Durham, NC, ³Psychiatry, University of Pittsburgh, Pittsburgh, PA

Background: Investigation of reward function has shown promise for elucidating the development and pathophysiology of depression. Adolescence is particularly informative for addressing this issue because it is the typical time of onset of depression, as well as a developmental period at which normative levels of reward-seeking behavior, reward-related brain function, and subjective positive affect change appreciably.

Methods: Converging methods included functional magnetic resonance imaging BOLD response to monetary reward, reward-related decision-making behavior, and 4-day experience sampling of mood using cell phones.

Results: In two samples, adolescents with major depressive disorder (MDD; age 8-17 years) exhibited less reward-related reactivity in the striatum (e.g., caudate t=4.55, p<.001) and more reactivity in regulatory areas such as the medial prefrontal cortex (mPFC) than healthy peers. A caudate region whose function distinguished depressed and healthy adolescents was associated with subjective positive affect in natural settings (R²=.22-.26). Behaviorally, in 211 11-year-old boys, reward-related decision-making distinguished those with depressive disorders and predicted onset of depressive disorders one year later (R²=.17). In terms of subjective experience, adolescents-but not children-with MDD experienced lower and less variable positive affect as measured by experience sampling in real-world environments. Finally, striatal and mPFC reactivity to reward in depressed adolescents predicted post-treatment severity and rate of anxiety symptom reduction (e.g., B=-.64, SE=.24, p<.01 for striatum) during an 8-week trial of cognitive behavioral therapy (CBT) or CBT plus selective serotonin reuptake inhibitor.

Conclusions: These findings support the clinical affective neuroscience claim that disrupted reward function is a key aspect of depressive disorders. Supported by K01 MH74769; NARSAD Young Investigator Award; R01 DA026222; P01 MH41712

355. Increased Striatal Activation during Reward Anticipation in Euthymic Bipolar Adults
Robin Nusslock¹,², Jorge R. C. Almeida², Erika E. Forbes², Amelia Versace², Edmund J. LaBarbara², Crystal Klein², Mary L. Phillips²
¹Northwestern University, Evanston, IL, ²University of Pittsburgh, Pittsburgh, PA

Background: Growing evidence from psychosocial and electrophysiological research indicates that bipolar individuals display a hyperresponsivity to reward relevant stimuli. Reward relevant life events have been demonstrated to trigger bipolar episodes, and bipolar individuals display excessive approach motivation during reward relevant tasks, as indexed by quantitative electroencephalography (EEG). The current study extends this research by examining reward-related brain function in euthymic bipolar adults and healthy controls. Hypotheses focused on activity in the ventral striatum given its sensitivity to the hedonic salience of stimuli.

Methods: Participants were 17 euthymic bipolar I adults and 16 individuals with no lifetime history of psychiatric disorder who underwent functional MRI scanning while engaged in a number-guessing task with monetary reward. Euthymic bipolar adults and controls were classified based on structured diagnostic interviews. Data were collected using a 3T Siemens Trio scanner. Analyses, conducted in SPM5, addressed group differences in BOLD response during reward anticipation.

Results: In line with prediction, individuals with bipolar disorder displayed increased right-sided ventral striatal activation during reward anticipation relative to control individuals (p <.01).

Conclusions: The observed increase in ventral striatal activation among bipolar individuals during reward anticipation is in line with growing evidence suggesting that bipolar disorder may be characterized by hypervisitivness to reward-relevant stimuli. This is contrasted with research suggesting that unipolar depression is characterized by blunted responsiveness in the ventral striatum during reward processing. Taken together, this suggests that MDD and bipolar disorder may be characterized by differential abnormalities in reward-related brain function.

Supported by RO1MH076971
**SYMPOSIUM**

Pharmacogenetics Imaging: A Method to Understand in-vivo Genetic Regulatory Effects

Friday, May 21, 2010 12:30 PM - 2:30 PM

Location: Bayside A - 4th Floor

Chair: Gonzalo Laje*

*Supported by Intramural Research Program - NIMH

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**356. Is Serotonin Transporter Expression Regulated by the Same HTR2A Variants Associated with Citalopram Response?**

**Gonzalo Laje**

**NIMH**

**Background:** A previous study found an association between genetic variants in HTR2A, which encodes the serotonin 2A receptor, and outcome of citalopram treatment. Citalopram binds the serotonin transporter (5-HTT) with high specificity. A measure of 5-HTT density in vivo can be obtained through PET imaging with the ligand [11C]DASB. The present study addresses the question of whether HTR2A marker alleles that predict treatment outcome also predict differences in 5-HTT density.

**Methods:** Brain levels of 5-HTT were assessed in vivo by positron emission tomography (PET) of [11C]DASB binding potential. DNA from 43 unmedicated volunteers was genotyped with 14 single nucleotide polymorphisms (SNPs) in and around HTR2A. Allelic association was tested in 8 brain regions of interest, with covariates to control for race and ethnicity.

**Results:** We detected allelic association between [11C]DASB binding potential in thalamus and 3 markers in a region spanning the 3’ untranslated region and second intron of HTR2A (rs7333412, p=0.000045; rs7997012, p=0.000086; rs977003, p=0.000069).

**Conclusions:** Genetic variation in HTR2A that is associated with antidepressant outcome is also associated with brain density of 5-HTT. While more work is needed to identify the actual functional variants, these results suggest a novel connection between HTR2A and 5-HTT that could shed light on the mechanism of action of SSRIs.

Supported by IRP/NIMH

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**357. Molecular Imaging of the 5-HT System: Behavioral and Genetic Influences**

**Gitte Moos Knudsen**

Rigshospitalet and University of Copenhagen

**Background:** Serotonergic neurotransmission is involved in the regulation of physiological functions such as mood, sleep, memory and appetite, and serotonergic dysfunction is implicated in the pathophysiology of a variety of neuropsychiatric disorders.

**Methods:** In vivo molecular imaging with emission tomography provides a tool to measure pre- and postsynaptic markers of serotonergic neurotransmission in healthy subjects and in patients with neuropsychiatric disorders.

**Results:** We recently found that the expression of a postsynaptic serotonergic marker, the 5-HT_2A_ receptor, is strongly genetically determined (Pinborg et al., 2008). This finding is consistent with the understanding of serotonin being profoundly involved in neurodevelopment, thereby also having possible implications for development of neuropsychiatric diseases. In 137 healthy individuals examined with PET, we were, however, unable to identify any association between 5-HT_2A_ receptor binding and three common polymorphisms in the 5HT2AR gene. We have found that in healthy individuals, a high score on the personality trait neuroticism, an important risk factor for major depression, is positively correlated with frontal-limbic 5-HT_1A_ receptor binding. This finding is now replicated in an independent sample of healthy twin subjects with high familial risk for developing affective disorder. These predisposed individuals also have reduced serotonin transporter binding in their dorsolateral prefrontal cortex.

**Conclusions:** These findings point to a neurobiological link between risk factors for development of affective disorder and the 5-HT transporter and 5-HT_2A_ receptor as biomarkers for vulnerability to this disorder.

Supported by Lundbeck Foundation, Danish Research Council, EU 6th Framework Programme

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**358. Epistasis in Brain Imaging with AKT1 and Pharmacogenetics of Cognition in Schizophrenia**

**Hao-Yang Tan,** Qiang Chen, Lauren Browne, Anthony G. Chen, Bhaskar Kolachana, Jose Apud, Venkata S. Mattay, Joseph H. Callicott, Daniel R. Weinberger

Clinical Brain Disorders Branch, National Institute of Mental Health, Bethesda, MD

**Background:** Epistasis or gene-gene interactions are likely to be a ubiquitous component of the genetic architecture of common diseases. Brain imaging affords unique opportunities in exploring the impact of genetic contributions on brain function, and may have advantages in detecting epistasis between genes working in close biologic relationships. Here, we extend recent work (Tan et al. JCI 2008) on the imaging genetics and pharmacogenetics of AKT1, a protein kinase implicated in schizophrenia, in lithium action, and in downstream signal transduction of dopamine receptors.

**Methods:** Functional imaging during the encoding phase of episodic memory (n=92) were examined in terms of epistatic interactions in AKT1, COMT and BDNF. A smaller replication sample of complex encoding during working memory (n=44) was studied. As findings might predict AKT1 rs1130233 could influence behavioral cognitive change (premorbid vs present IQ) associated with disease and treatment, cross-sectional observations from schizophrenia patients were examined in terms of genetic interactions with mood stabilizers (n=47) and antipsychotics (n=111).

**Results:** The imaging data suggest that AKT1, COMT and BDNF act as interacting partners in hippocampal neural function during memory encoding (p<0.05 corrected within hippocampal region-of-interest). Extending these findings to behavioral data in schizophrenia patients, AKT1 variation predicted a moderation of cognitive decline in relation to Lithium or Valproate treatment (p<0.005); this variant was also associated with a dose- response relationship with antipsychotics (p<0.05).

**Conclusions:** In addition to statistical relationships in functional brain maps representing the molecular genetics of memory processing, AKT1 may be of significance to behavioral cognitive deficits and its treatment in schizophrenia. Supported by NIMH Intramural Research Program

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**359. Neuroimaging and Genetics of Antidepressant Response**

**Francesco Benedetti**

Department of Clinical Neurosciences, Istituto Scientifico Universitario Ospedale San Raffaele, Milano, Italy

**Background:** Gene polymorphisms which influence the activity of brain monoaminergic systems and of the biological clock influence core psychopathological features of mood disorders and antidepressant response to treatment. They could then influence the changes in brain metabolism and function which parallel antidepressant response.

**Methods:** Inpatients with major depression underwent (1) BOLD fMRI and (2) single voxel proton spectroscopy before and after antidepressant treatment. The cognitive activation paradigm was based on a go/no-go task with morally
Methods: Association with antidepressant response have had mixed results. Risk of depression in general adult populations. In turn, studies examining its but by and large the less active Met66 allele does not appear to increase the been associated with alterations in hippocampal function and morphology, but by and large the less active Met66 allele does not appear to increase the risk of depression in general adult populations. In turn, studies examining its association with antidepressant response have had mixed results.

Conclusions: Brain imaging techniques can detect in which brain areas genetic polymorphisms exert their pharmacogenetic role. Supported by Italian Ministry of university and scientific research.

**Supported by NIH, NIMH, NCCAM**

**Supported by R01MH54846; P50MH60451**

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**360.-367. Late Breaking Oral**

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

**SYMPOSIUM**

**The Neurobiology of Late- Life Mood Disorders: Biomarkers and Aging**

Friday, May 21, 2010 3:00 PM - 5:00 PM

Location: Nottoway - 4th Floor

Chair: Helen Lavretsky*

Co-Chair: Warren D. Taylor**

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**368. The Brain-Derived Neurotrophic Factor (BDNF) Val66Met Polymorphism in Late-Life Depression: Relationship with Clinical Factors and Biomarkers**

Warren D. Taylor

Duke University

Background: Brain-derived neurotrophic factor (BDNF) may have an important role in the pathogenesis of depression and the antidepressant response, hypothetically through its role in modulating synaptic plasticity and neuronal connectivity. In younger adult subjects, this polymorphism has been associated with alterations in hippocampal function and morphology, but by and large the less active Met66 allele does not appear to increase the risk of depression in general adult populations. In turn, studies examining its association with antidepressant response have had mixed results.

Methods: This is a cohort study of elderly depressed and nondepressed subjects. Study participants completed clinical assessments, cognitive assessments, cranial 1.5T MRI, and provided blood for genotyping.

Results: The Met66 allele may occur more frequently in older, more severely depressed populations. It is also associated with clinical and neuroanatomic findings associated with late-life depression, and these associations differ from what is observed in younger adult populations.

Conclusions: The BDNF Met66 allele may contribute to the pathogenesis of depression in older populations through several potential mechanisms. Importantly, these findings are different than what is observed in younger adult populations, which emphasizes the need for a better understanding of the interaction between genetic differences, life experiences, and aging and how that may influence the development of depression.

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**369. Age-Dependent Alterations of Astrocyte-Associated Intercellular Adhesion Molecule 1 Immunoreactivity in the Orbitofrontal Cortex of Older Subjects with Major Depression**

Jose Javier Miguel-Hidalgo

Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS

Background: Vascular and immune alterations in the prefrontal cortex may contribute to the etiology of major depression in elderly subjects. Since glial cells mediate immune and inflammatory responses in the brain, depression-specific immune alterations might be associated with glial cells in relevant regions of the prefrontal cortex. Intercellular adhesion molecule 1 (ICAM-1), a major inflammatory mediator in the vascular endothelium and astrocytes, could be altered in geriatric depression, but little is known about its age-dependent expression in subjects with depression and its relationship to the expression of astrocyte markers.

Methods: Immunohistochemistry for ICAM-1 and the astrocyte marker GFAP was applied to histological sections of the postmortem orbitofrontal cortex from 19 non-psychiatric control subjects and 18 subjects with major depression. Nine subjects in each group were over 60 years old. We measured the percentage of gray matter covered by ICAM-1 (area fraction of ICAM-1) in blood vessels and in extravascular accumulations of ICAM-1 immunoreactivity. Association of extracellular ICAM-1 to GFAP-positive astrocytes was investigated by double-labeling immunofluorescence.

Results: Both vascular and extravascular area fractions of ICAM-1 immunoreactivity were lower in depressives than in controls. Controls older than 60 experienced a dramatic increase in extravascular ICAM-1 immunoreactivity, but this increase was significantly attenuated in elderly MDD subjects. Most extracellular ICAM-1 immunoreactivity was coexistent with GFAP-immunoreactive astrocytes.

Conclusions: There is a significant attenuation of extravascular and vascular ICAM-1 immunoreactivity in elderly subjects with major depression that might point to a specific alteration of astrocyte-associated immune function in the aging orbitofrontal cortex.

Supported by R01MH7701; MH60451; MH67996; NARSAD

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**370. Amygdala Activation to Emotional Faces in Geriatric Depression**

Howard J. Aizenstein

University of Pittsburgh

Background: Previous studies have demonstrated amygdala activation when individuals view emotional faces. In mid-life depression the amygdala shows increased activation pre-treatment, which predicts treatment response, and ‘normalizes’ in response to treatment. With aging, the amygdala appears to have a diminished response to emotional faces. The aim of the current study was to identify the pattern of amygdala response in geriatric depression. A diminished response would account for the ‘accelerated aging’ brain changes in geriatric depression.
in geriatric depression, while an increased response would emphasize the neurobiological similarities to midlife depression.

**Methods:** Subjects included 27 individuals with late-life major depression and 21 elderly individuals without depression. Depressed subjects underwent fMRI scanning with a facial expression task before starting SRI pharmacotherapy, and 12-16 weeks later. Non-depressed subjects were scanned at 2 time-points 12 weeks apart.

**Results:** As expected, there was robust bilateral amygdala activation across the whole group (T(47)>5.57, p<.01, corrected). Contrary to the results in mid-life depression, there was lower amygdala activation in the patients relative to the controls – this difference, however, was only marginally significant (t(46)=1.68, p<0.05, uncorrected). Despite, the relatively low amygdala activation prior to treatment, amygdala activity predicted treatment response, and showed decreased activation after treatment (t(24)>2.49, p<0.01 uncorrected).

**Conclusions:** In conclusion, the amygdala reactivity to emotional faces appears less prominent in late-life than in midlife depression, signaling accelerated aging brain changes. However, the relative decrease in amygdala reactivity following successful treatment remains a marker of antidepressant treatment response, similar to results obtained in mid-life depression.

Supported by NIH R01 MH076079, R21 NS060184, P50 AG005133, P30 MH71944 and the John A. Hartford Center of Excellence in Geriatric Psychiatry.

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**371. Molecular Imaging in Geriatric Depression**

**Gwenn Smith**

John Hopkins University, Baltimore, MD

**Background:** Over the past decade, positron emission tomography (PET) molecular imaging methods have been incorporated into treatment studies to understand the neurobiology of geriatric depression. This strategy provides a unique opportunity to assess the functional integrity of neurochemical systems and the capacity of the brain to compensate for age and disease related (neurochemical and neuropathological) changes. These studies identified the functional neuroanatomy of geriatric depression and antidepressant treatment response. Increased cortical glucose metabolism was observed in patients relative to controls. The hypermetabolic regions overlap with areas of volumetric decreases, as well as with brain regions that comprise the ‘default network’. Decreased metabolism was observed in the same regions after antidepressant interventions. The magnitude of decrease in metabolism was correlated with improvement of mood and cognitive symptoms.

**Methods:** Studies are in progress to investigate the underlying pathophysiology by studying serotonin transporter (SERT) occupancy by a selective serotonin reuptake inhibitor (SSRI, citalopram) and beta-amyloid (Aβ) deposition.

**Results:** Greater SERT occupancy is correlated with greater improvement of mood symptoms, in regions that are hypermetabolic and are affected by citalopram treatment. Aβ deposition may be associated with the metabolic alterations and with persistent cognitive impairment after mood symptom remission. Studies performed thus far support the hypotheses of lower SERT availability and greater Aβ deposition in patients relative to controls. Greater SERT occupancy and less Aβ deposition is associated with greater improvement in mood and episodic memory, respectively.

**Conclusions:** The ultimate goal of these studies is to obtain a mechanistic understanding of treatment resistance in geriatric depression.

Supported by NIH/NIMH 64823
before and after CBT, and have examined the ERN following anxiety/fear provocation in spider phobics.

Results: The ERN demonstrates excellent test-retest reliability. Pediatric patients with OCD have increased ERNs, and treatment-related reductions in OCD symptoms are unaccompanied by reductions in the ERN. Finally, provocationss that increase state-levels of fear and anxiety had no impact on the ERN.

Conclusions: The ERN is a stable, trait-like measure of neural activity related to response monitoring. Hyperactive error-processing, reflected in an increased ERN, is a promising endophenotype for OCD. Unresolved questions and future directions in this area will be discussed.

Supported by MH69047-02

374. Increased Error-Related Brain Activity and Age at Onset in Pediatric Obsessive-Compulsive Disorder
Gregory L. Hanna

University of Michigan

Background: Abnormalities in frontostriatal circuits, including the anterior cingulate cortex (ACC), have been consistently reported in studies of obsessive-compulsive disorder (OCD). The error-related negativity (ERN/Nc), which is generated by the ACC, has been found to be increased in both adults and children with OCD. This study was done to assess medial frontal event-related potentials (ERPs) and their behavioral correlates in pediatric OCD.

Methods: We ascertained 20 probands with a lifetime diagnosis of OCD, 18 unaffected siblings of OCD probands, and 28 healthy controls ranging in age from 8 to 17 years. OCD probands were directly assessed with 2 semi-structured diagnostic interviews. All subjects were assessed with parent-report questionnaires and youth self-report questionnaires. ACC function was assessed with the ERN and error positivity (Pe) while subjects performed an Eriksen flanker task.

Results: ERN amplitude was significantly higher in OCD subjects than controls. ERN amplitude had significant correlations with age in all subjects and with age at obsessive-compulsive symptom (OCS) onset in the OCD subjects. Pe amplitude had significant correlations with OC and other internalizing symptom ratings in all subjects.

Conclusions: The results provide further evidence of increased error-related brain activity in pediatric OCD, which may be associated with severity and age at onset of OCS. A larger sample will be necessary to determine whether either ERP is increased in the unaffected siblings of OCD probands.

Supported by International OCD Foundation

375. Neural Imaging Markers for Obsessive Compulsive Disorder in Children and Adolescents
Andrew R. Gilbert1,2, Jorge RC Almeida3, Dalila Akkal3, David Mataix-Cols4, David Rosenberg5, Mary L. Phillips6

1Psychiatry, Mt. Sinai School of Medicine, New York, NY, 2Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, 3Helsinki University of Technology, Helsinki, Finland, 4Institute of Psychiatry, London, United Kingdom, 5Wayne State University School of Medicine, Detroit, MI

Background: OCD has a frequent onset in childhood and adolescence. Regulatory control deficits have been described in adults and youth with OCD and in individuals at risk for OCD but their neural correlates remain to be fully elucidated.

Methods: We conducted a series of studies probing frontostriatal pathways underlying regulatory control and previously implicated in the pathophysiology of OCD. Pediatric OCD subjects [OC] (n=18) were compared to healthy controls [HC] (n=18). Using functional magnetic resonance imaging (fMRI), subjects underwent a symptom provocation paradigm (contamination/washing and symmetry/ordering) and a response inhibition task (go/no-go). Voxel based morphometry (VBM) was used to measure gray matter (GM) in subjects. A separate VBM study of OC (n=10), unaffected siblings (n=10) and HC (n=10) was also carried out.

Results: During provocation, we found significantly less neural activity (p<0.05) (contamination provocation) and GM (p<0.05) in dorsolateral prefrontal cortex [DLPFC] and orbitofrontal cortex [OFC] and right putamen in OC compared to HC. There were significant negative correlations (P<0.05) between contamination symptom severity and DLPFC neural activity and OFC GM. During the go/no-go task, OC showed less activation than HC (p<0.05) in right medial frontal gyrus and left putamen. Our VBM study found significantly less left putamen GM in unaffected siblings compared to OC (p<0.05).

Conclusions: We identified structural and functional alterations in components of frontostriatal circuitry underlying regulatory control among OC versus HC subjects. Neural correlates of regulatory control deficits may present illness markers early in the course of OCD and may be present in those at risk.

Supported by 1 KL2 RR024154-03

SYMPOSIUM
Specificity of Corticolimbic Abnormalities in Adolescents with Major Mood Disorders and Borderline Personality Disorder
Friday, May 21, 2010 3:00 PM - 5:00 PM
Location: Borgue - 3rd Floor
Chair: Antonia S. New
Co-Chair: Wayne Drevets*

*Supported by NIMH Intramural Research Program

376. The Structural Development of the Limbic System in Healthy Children and Adolescents
Philip Shaw
NIH/NIMH, Bethesda, MD

Background: Understanding the development of the limbic system in healthy children and adolescents is a prerequisite for interpreting anomalies that are found in major depressive disorder and related disorders.

Methods: A review of longitudinal magnetic resonance neuroanatomic studies, focusing on data from the Intramural NIMH study of typical child development. This includes 764 neuroanatomic scans acquired prospectively on 375 healthy children. Using computational neuroanatomy measures of components of the limbic system were extracted, including limbic cortical thickness measures and volumes of the amygdala and hippocampus.

Results: Within the cortical components of the limbic system there is a tight link between underlying cytoarchitecture and the complexity of developmental trajectories. Allocortical regions (such as the putiform cortex) show simple linear growth; isocortical regions (e.g. the lateral orbitofrontal) show the most complex trajectory with childhood increase, adolescent decrease and then a transition to adult stability; and transitional cortical regions (e.g. the anterior cingulate gyrus) show trajectories of intermediate complexity. Initial volumetric analyses of the allocortical hippocampus and amygdala suggest there is little volume change over development.

Conclusions: Understanding the course of typical limbic development allows us to conceptualize mood disorders as reflecting deviations away from the template of healthy neurodevelopment.

Supported by NIH Intramural Program
377. Structural Neural Correlates of Depressed Mood in Normal Healthy Children

Aaron Boes

University of California- San Diego, San Deigo, CA

Background: Adults with major mood disorders and borderline personality disorder have neuroanatomical differences in corticalic regions in association with these disorders. It is not yet known whether these structural differences act as biological markers of vulnerability for these disorders. The aim of this study was to evaluate whether two of these regions, the rostral anterior cingulate cortex (rACC) and amygdala, correlate to depressive symptoms in healthy children and adolescents. We hypothesized that depressive symptoms would correspond to decreased rACC volume and increased amygdala volume. In addition, we examined how a positive family history of depression affects this relationship.

Methods: We recruited from the community one hundred twelve normal healthy children (59 boys, 53 girls), age 7 to 17, without a current diagnosis or history of depression or other psychiatric illness. Mood symptoms were collected using the Pediatric Behavior Scale, a parent- and teacher-reported questionnaire. Volumetric measures of the rACC and amygdala were generated using structural magnetic resonance imaging (MRI).

Results: There was a negative correlation of rACC volume and depressive symptoms in boys. In girls there was a positive correlation of amygdala volume and depressive symptoms. In both groups these correlations were more robust when limited to individuals with a positive family history of depression.

Conclusions: These findings lend support to the notion that the structure of the rACC and amygdala may act as biologic markers of vulnerability or trait markers of depression.

Supported by NIH: 1 RO1 DE01 14399 01 A1

378. An Altered Developmental Trajectory of Frontotemporal Connectivity in Bipolar Disorder

Fei Wang, Erin Edmiston, Esther Hur, Jessica H. Kalmar, Fay Y. Womer, Lara G. Chepenik, Hilary P. Blumberg

Yale School of Medicine, New Haven, CT

Background: Emerging evidence supports the presence of abnormalities in the neurodevelopmental trajectories of frontotemporal (FT) gray matter structures, including the amygdala and ventral prefrontal cortex (VPPC), in adolescence and young adulthood in bipolar disorder (BD). Taken together with increasing evidence for abnormalities in the frontotemporal white matter (FTWM) connecting the VPPC to the amygdala in BD, these data suggest the possibility of an altered trajectory of FTWM development in BD.

Methods: One hundred adolescents and adults with BD and one hundred and thirty healthy comparison adolescents and adults participated in diffusion tensor imaging and in functional magnetic resonance imaging performed at thirty healthy comparison adolescents and adults participated in diffusion imaging and in functional magnetic resonance imaging performed at.

Results: Patterns of FTWM fractional anisotropy increases across adolescence and young adulthood differed between the groups with and without BD. The structural connectivity differences were associated with parallel patterns of differences in FT functional connectivity.

Conclusions: The data suggest altered developmental trajectories of FTWM over adolescence and young adulthood in BD that are associated with disruptions in functional connectivity. Implications for understanding the pathophysiology of BD, as well as for methods to detect and treat the disorder will be discussed. Preliminary data suggesting differences in the developmental patterns between BD and major depressive disorder will also be discussed.

Supported by R01MH69747, R01MH670902, R11DA024856, RC3MH088366, NARSAD, Klingenstein Foundation, Women's Health Research at Yale, VA REAP

379. Anterior Cingulate Volume Abnormalities in Adolescents with Borderline Personality Disorder - A Potential Biomarker?

Marianne Goodman

J J Peters VAMC and Mount Sinai School of Medicine

Background: Data exists for reduced cingulate gyrus (ACG) volume in adults with borderline personality disorder (BPD) (Hazlett et al, 2005), however published data on ACG volume in adolescent BPD is minimal. Whittle et al. (2009) showed decreased left ACG volume in a sample of 15 BPD adolescents with Axis 1 co-morbidities.

Methods: Hospitalized BPD adolescents were recruited and diagnosed for Axis I (SCID I) and BPD (Zan-BPD and SCID II). Structural 3T MRI was obtained in 13 adolescents with major depressive disorder (MDD) and BPD (mean age=15.9, 11 girls, 2 boys) and 13 age- and sex-matched healthy adolescents (mean age=16.2, 9 girls, 4 boys). Brodmann area (BA) methods were used to examine cingulate volume, similar as in our BD adults (Hazlett et al. 2005).

Results: In the ACG, MDD-BPD adolescents had smaller relative volume in BA24 compared with the healthy adolescents (Group x Cingulate BA area interaction, F[4,96]=3.43, p=0.03, Huynh-Feldt adjusted degrees of freedom) but they do not differ in the other BA within the cingulate (BA25, 31, 23, or 29), or in overall relative cingulate volume. In BA 24, MDD/BPD+ adolescents displayed a reduction in gray but not white matter (Group x BA area x Matter type interaction (F[4, 96]=2.58, p=0.048, Huynh-Feldt adjusted degrees of freedom).

Conclusions: Smaller BA24 volume may be a potential biomarker for BPD as it appears to be present in adolescence and found in a different sample of adult BPD. Supported by Mount Sinai GCRC pilot funds

SYMPOSIUM

Glucocorticoid Receptor (GR) Chaperone-Mediated Plasticity in Health and Disease

Friday, May 21, 2010 3:00 PM - 5:00 PM

Location: Bayside BC - 4th Floor

Chair: Hussein Manji*
Co-Chair: Jing Du**

*Supported by Johnson &Johnson Pharmaceutical and Research Development L.L.C.
**Supported by NIMH intramural

380. FKBP5 - A Common Candidate Gene for Stress-Related Psychiatric Disorders?

Elisabeth B. Binder1,2

1Max-Plank Institute of Psychiatry, Munich, Germany, 2Psychiatry and Behavioral Sciences and Human Genetics, Emory University School of Medicine, Atlanta, GA

Background: FK 506 binding protein 51 or FKBP5 is a co-chaperone of hsp90 which regulates glucocorticoid receptor (GR) sensitivity. FKBP5 mRNA and protein expression are induced by GR activation via intronic hormone response elements and this provides an ultra-short feedback loop for GR-sensitivity.

Methods: We will present data from FKBP5 gene expression in peripheral blood and their correlation with endocrine measures as well as genetic association studies and gene x environment interactions in samples from three different ethnic backgrounds to support a central role of FKBP5 in stress-related psychiatric disorders.

Results: Gene expression studies in peripheral blood show that FKBP5 mRNA expression is correlated with the cortisol response in the Trier Social Stress Test
as well as the level of experienced child abuse. Peripheral upregulation of FKBP5 mRNA by dexamethasone is significantly reduced in patients with acute unipolar depression as compared to controls. A pregnancy associated upregulation of this gene is also significantly reduced in women with peripartum depression. Interactions of polymorphisms within this gene with childhood abuse on stress-related psychiatric disorders such as PTSD and depression are seen in an African American, European- as well as Nepalese cohort.

**Conclusions:** A number of experiments in different samples suggest that peripheral blood expression of FKBP5 mRNA or its induction by GR-stimulation may be a sensitive marker for GR sensitivity changes related to psychiatric disorders or trauma exposure. The transethnic replications of gene x early trauma interactions of FKBP5 polymorphisms with stress-related psychiatric disorders or trauma exposure. The transethnic replications of gene x early trauma interactions of FKBP5 polymorphisms with stress-related psychiatric disorders or trauma exposure. The transethnic replications of gene x early trauma interactions of FKBP5 polymorphisms with stress-related psychiatric disorders or trauma exposure. The transethnic replications of gene x early trauma interactions of FKBP5 polymorphisms with stress-related psychiatric disorders or trauma exposure. 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SYMPOSIUM
Glutamatergic System Modulators as Novel Therapeutic Agents for Schizophrenia and Bipolar Disorder
Friday, May 21, 2010 3:00 PM - 5:00 PM
Location: Oak Alley - 4th Floor
Chair: Anantha Shekhar* Co-Chair: Amit Anand

*Supported by NIH R01s MH 052619 and MH065702.

384. Interactions of Glutamatergic Amygdalar Afferents with GABA Cells at Key Corticolimbic Loci
Francine Benes
Harvard Medical School, Belmont, MA

Background: The development of schizophrenia is associated with dysfunction of GABAergic neurotransmission within corticolimbic regions of the brain. The basolateral nucleus of the amygdala (BLA) may be particularly important for the pathophysiology of this disorder because it provides a dense innervation to the anterior cingulate cortex (ACCx) and hippocampus (HIPP) where postmortem studies have demonstrated many structural and molecular abnormalities, particularly in the GABA system. It has been postulated that GABAergic dysfunction may be related, at least in part, to an increased flow of excitatory glutamatergic activity from the BLA to layer II of ACCx and sectors CA3/2 of the hippocampus. During the late post-weaning and early adult periods, the BLA innervation of the cortex dramatically increases, as it forms contacts with dendritic spines and shafts in the neuropil.

Methods: Using both light and electron microscopic immunocytochemistry, BLA fibers were co-localized with GABAergic interneurons in rat mPFC between birth and adulthood.

Results: BLA fibers were seen forming increased numbers of appositions with dendritic shafts of GABA-positive neurons (35.5%) and the spines of non-GABAergic neurons (32%) between P0-P120. Synaptic membrane specializations were only present when BLA fibers formed contacts with dendritic spines, but not dendritic shafts.

Conclusions: Taken together, these observations suggest that the interactions of BLA fibers with GABAergic elements increase postnatally and are predominantly non-synaptic in nature. In studies using our rodent model for postmortem findings in schizophrenia, BLA projections appear to use kainate receptors to influence the firing pattern of GABAergic interneurons.

Supported by MH42261, MHNS 31862, MH77175

385. Suppressing Glutamate Release: Preclinical Evidence for Antipsychotic and Antidepressant Effects
Gerard J. Marek
Neuroscience Development, Abbott Laboratories, Abbott Park, IL

Background: While metabotropic glutamate2/3 receptor (mGluR2/3) agonists have been successfully tested in the clinic for schizophrenia and generalized anxiety disorder, mGluR2 activation has not been widely explored with respect to predicting efficacy in depression. The most prominent effects of mGluR2 agonists is to suppress glutamate release via activation of mGlu2 autoreceptors. Since adenosine A1 receptors act similarly in suppressing glutamatergic neurotransmission in limbic forebrain regions, we examined the effects of activating adenosine A1 receptors in a preclinical antidepressant drug screen.

Methods: Adult male Sprague-Dawley rats were water restricted and trained to lever press for water on a differential-reinforcement-of-low rate 72-s (DRL 72-s) operant schedule. After stable performance was reached, the rats were injected with the adenosine A1 receptor agonist CHA (0.0156-0.125 mg/kg) and/or the adenosine A1 receptor antagonist (0.031 mg/kg) 60 min prior to their session.

Results: The adenosine A1 agonist CHA increased the reinforcement rate, decreased the response rate and exerted a rightward shift in the interresponse time (IRT) distributions in a dose-dependent manner. DPCPX exerted a modest but significant increase in the response rate. DPCPX also blocked the “antidepressant-like” effects of CHA.

Conclusions: The present results demonstrate that activation of adenosine A1 receptors appears to decrease impulsivity and results in antidepressant-like effects on DRL 72-s behavior. These results are consistent with the hypothesis that suppressing pathologically increased glutamate release may result in both antidepressant and antipsychotic like effects. Thus, agents which suppress glutamate release like mGluR2 agonist or mGluR2 potentiators may have utility in both manic and depressive episodes of bipolar disorder.

Supported by R01 MH628186 and K08 MH01551

Alan Breier
Indiana University School of Medicine, Indianapolis, IN

Background: Several lines of investigation have supported altered glutamatergic function in schizophrenia. This evidence includes the findings that agents, such as phencyclidine and ketamine which antagonize the glutamate N-methyl-D-aspartate (NMDA) receptor, produce a clinical state that resembles many features of schizophrenia including cognitive dysfunction, negative symptoms and hallucinations. Also, agents that modulate glutamate neurotransmission have been shown in both preclinical and clinical models to mitigate the neurochemical and behavioral effects of NMDA antagonism. Moreover, it has been hypothesized that excessive glutamatergic activity may have excitotoxic effects that might contribute to the progressive cortical erosion observed during the early stages of schizophrenia.

Methods: In this presentation, studies that address the role of altered glutamatergic function in schizophrenia will be reviewed. In addition, several agents that affect glutamatergic function that have been assessed in clinical trials of schizophrenic patients will be examined. Lastly, the hypothesis that early intervention with drugs that modulate glutamatergic neurotransmission may have neuroprotective (i.e., anti-excitotoxic) effects and arrest progressive cortical erosion and thereby positively modify the long term trajectory of the illness will be explored.

Results: Results from completed clinical trials including double blind randomized proof of concept studies will be presented.

Conclusions: The data presented will make the case that glutamate offers a desirable target for future antidepressant drug development and an important focus for future research is disease modification and the prevention of clinical duration through early intervention with neuroprotective agents.

Supported by Eli Lilly - salary support

387. Memantine Augmentation of Lamotrigine Incomplete Response in Bipolar Depression: A Double Blind Placebo Controlled Trial
Amit Anand
Indiana University School of Medicine, Indianapolis, IN

Background: It is unclear whether strategies for developing glutamatergic treatments for mood disorders should be focused on pre-synaptic or postsynaptic mechanisms or a combination of the two. Lamotrigine, an anticonvulsant which decreases glutamate release, has been shown to be effective in bipolar
388. The NIMH Perspective on Translational Cognitive Neuroscience

Bruce Cuthbert

NIMH, Bethesda, MD

Background: The parsing of schizophrenia symptoms into separate clusters of positive symptoms, negative symptoms, and cognitive disorganization is but one illustration of the marked heterogeneity of psychiatric syndromes. Conversely, recent genetic studies reveal that schizophrenia and bipolar disorder exhibit considerable overlap in genetic risk in spite of overtly different phenotypic presentations. More broadly, problems of co-morbidity, over-specified diagnoses, and reified categories are pervasive problems throughout current psychiatric nosologies. In recognition of such issues, the National Institute of Mental Health has started an initiative termed the Research Domain Criteria (RDoC) project to develop new ways of classifying patients in clinical research studies, based on the identification of fundamental dimensions of functioning and the translation of genetic, neurobiological, and behavioral research on these dimensions to an understanding of disorder.

Methods: n/a

Results: n/a

Conclusions: Thus, classification might be based upon a specified polymorphism, performance in an experimental task, or responses in a neuroimaging paradigm rather than traditional nosological status. CNTRICS represents in many respects a model for the RDoC approach, and the current NIMH perspective on translational research in cognitive neuroscience will be discussed in terms of these two initiatives.

389. Translational Development of the Relational and Item-Specific Encoding (RISE) Long Term Memory Task

J. Daniel Ragland1, Charan Ranganath2, Deanna Barch3, Steve Dakin4, Jim Gold5, Brittaney Haley1, Phil Harvey6, Keefe Richard7, I. Kovacs8, Steve Luck2, Angus McDonald9, Steven Silverstein10, Milton Strauss11, Cameron Carter1

1Psychiatry and Behavioral Sciences, University of California at Davis, Sacramento, CA, 2Psychology, University of California at Davis, Sacramento, CA, 3Washington University, St Louis, MO, 4UCL Institute of Ophthalmology, London, United Kingdom, 5University of Maryland, College Park, MD, 6Emory University, Atlanta, GA, 7University of California at Los Angeles, Los Angeles, CA, 8Rutgers University, Piscataway, NJ, 9University of Minnesota, Minneapolis, MN, 10UMDMJ - Robert Wood Johnson Medical School, Newark, NJ, 11Case Western Reserve, Cleveland, OH

Background: The RISE is an episodic long term memory (LTM) task designed to assess item and relational memory. Item memory refers to memory for individual stimuli or elements irrespective of contemporaneously presented context or elements, and relational memory refers to memory for stimuli/elements and how they were associated with coincident context, stimuli or events.

Methods: The presentation will begin with a review of these two memory constructs, describing their neural and cognitive underpinnings, and providing initial evidence that individuals with schizophrenia may experience a specific deficit in relational memory with relatively unimpaired item-specific memory under certain task conditions. This background information will be followed by a discussion of the challenges and accomplishments experienced as the RISE was translated from a cognitive neuroscience task developed in healthy undergraduates to an instrument that can be validly and reliably administered to patients with schizophrenia in a clinical trials context.

Results: Challenges included constructing parallel forms to reduce practice effects, avoiding ceiling effects in healthy participants, and equating task difficulty across memory conditions. Data will be presented illustrating how a change in stimulus modality (i.e., a change from visual objects to word stimuli) is helping to accomplish these goals.

Conclusions: The process of translating the RISE from a basic to a clinical measure has revealed challenges both expected (e.g., simplifying instructions, reducing task demands) and unexpected (e.g., effects of stimulus modality) that may help to inform future task development.

Supported by R01MH084826
390. Translation and Development of a Goal Maintenance Task for Clinical Applications

Angus MacDonald1, Deanna M. Barch2, Cameron S. Carter3, Steven Dakin4, James Gold5, Ilona Kovacs6, Steve Luck7, J. Daniel Ragland3, Charan Ranganath9, Steven Silverstein8, Milton Strauss10

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Background: Context processing is a form of goal representation in which the context of a cue stimulus must be represented and maintained to provide top-down support for a subsequent action. While context processing tasks, such as expectancy variants of the AX task, have been used in experimental studies in schizophrenia, no one has examined whether such a paradigm is sufficiently robust for clinical use.

Methods: 5 variants of the Dot Pattern Expectancy task were performed by the CNTRACS sample of 150 schizophrenia patients and 150 healthy controls. A dot pattern is defined as a valid cue (“A”) and another pattern a valid probe (“X”). Three levels of expectancy for the valid A-X sequence were tested (70%, 65% and 60% of trials). Rare B-X sequences (12% of trials) were used to examine participants’ capacity to maintain and use the context of the invalid cue to avoid false alarms. The delay between stimuli was varied to derive an optimal balance between task duration and sensitivity to patient deficits.

Results: An intermediate level of expectancy (65% A-X trials) and a longer delay between the cue and probe provided an interaction consistent with a specific deficit in context processing, and this condition had more favorable psychometric properties than variants with a shorter delay or a weaker expectancy (60% A-X trials). We also compared the internal consistency, sensitivity, and length across variants.

Conclusions: A new generation of context processing tasks may allow the evaluation of this cognitive construct in a manner suitable for clinical assessment and medication trials.

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391. Translational Development and Psychometric Comparison of Two Visual Integration Tasks

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Background: Visual integration, or the ability to efficiently bind visual features into object representations, is impaired in many people with schizophrenia, as reported in clinical descriptions and experimental studies over the past 50 years. The purpose of this study was to optimize and compare the psychometric characteristics of two measures of visual integration that met criteria for clinical trial utility as identified by the CNTRICS initiative.

Methods: Data were collected at the 5 sites of the CNTRACS consortium, using its standardized substance abuse screening, diagnostic, symptom rating, and functional assessment procedures. Seventy-five schizophrenia patients and 75 controls completed two measures of contour integration: a) the Jittered Orientation Visual Integration (JOVI) task, in which difficulty in judging the left-right orientation of a single closed contour is increased across multiple conditions by randomly varying the jitter of the individual contour elements relative to their original position; and b) the Spatial Offset Visual Integration (SOVI) task, in which difficulty level was manipulated by varying the spacing between individual contour elements.

Results: Results on the JOVI are consistent with past data on this measure. Comparisons of the effect sizes on the conditions discriminating patients and controls will be reported. The SOVI also discriminated patients from controls.

Conclusions: Both the JOVI and SOVI discriminated patients from controls. The strengths and weaknesses of each task, in terms of between-groups effect size, within-subject variability, process-specificity, generalized deficit issues, reliability, practice effects, time, and suitability for clinical trials will be discussed.

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393. Decreased Number of Parvalbumin and Cholinergic Interneurons in the Striatum of Individuals with Tourette Syndrome

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Background: GABAergic neurons containing parvalbumin in the cerebral cortex, hippocampus and basal ganglia modulate motor activity and cognitive functions. These neurons are particularly vulnerable to maldevelopment or die during their extended period of postnatal maturation. In the striatum, parvalbumin interneurons form a powerful inhibitory network driven by cortex and thalamus and set the pace of cortico-basal ganglia oscillations in synchronous neuronal activity. Parvalbumin interneurons down-regulate the firing of striatal projection neurons, the medium spiny neurons (MSN), directly or through the mediation of basal ganglia cholinergic interneurons.

Methods: To assess whether the striatal inhibitory network is altered in Tourette Syndrome (TS), we estimated the number of different types of striatal interneurons and MSNs in the postmortem brains of 5 TS subjects as compared with matched normal controls (NC) by unbiased stereological analyses.

Results: TS patients demonstrated a 50-60% decrease of both parvalbumin+ and choline acetyltransferase+ cholinergic interneurons in the caudate and putamen, but not in the nucleus accumbens. Cholinergic interneurons were decreased in the associative and sensorimotor territory but not in the limbic regions of the striatum. In NC brains, cholinergic neurons formed a gradient, with highest numbers in associative, intermediate in sensorimotor and lowest in limbic regions; in TS, this gradient was absent. No significant difference was present in medium-sized calretinin interneurons, MSNs and total neurons.

Conclusions: The deficiency in parvalbumin and cholinergic interneurons in TS may result in an impaired cortico/thalamic control of striatal neuron firing and aberrant cortico-basal ganglia oscillatory activity.

394. Anatomical Disturbances of the Cerebellum in Persons with Tourette Syndrome

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Background: Tourette Syndrome (TS) is defined by the presence of semi-involuntary movements and sounds. Disturbances of cortico-striato-thalamo-cortical (CSTC) circuits are implicated in TS and comorbid Obsessive Compulsive Disorder (OCD). Caudate nucleus volumes are smaller in persons with TS and regional cortical thinning is present in direct proportion to tic severity. Numerous studies have identified the cerebellum as an integral component of motor and language control while tracing studies link cerebellum to CSTC circuits. Few studies, however, have investigated a cerebellar contribution in TS.

Methods: MRI scanning was conducted in 163 persons with TS and 147 control participants. Multivariate linear regression models were used to explore effects on cerebellar surface morphology and underlying volumes for the main diagnosis effects of TS as well as comorbid OCD and Attention-Deficit/ Hyperactivity Disorder (ADHD). Additionally, correlations of symptom severity with cerebellar morphology were assessed.

Results: The TS group demonstrated reduced volumes of the cerebellar hemispheres bilaterally that derived primarily from reduced gray matter in Crus I and lobules VI, VIIb, and VIIIa. These decreased regional volumes accompanied increasing tic symptom severity and motoric disinhibition as demonstrated by a finger tapping test. Males had reduced volumes of these same regions compared with females, irrespective of diagnosis. Comorbid OCD was associated with relative enlargement of these regions in proportion to the increasing severity of OCD symptoms.

Conclusions: The cerebellum is involved in the pathogenesis of TS and tic-related OCD. Baseline gender differences in cerebellar morphology may in part account for the more prevalent expression of TS in males.

395. Deficits in Prepulse Inhibition Persist in Individuals Whose Tourette Syndrome has Remitted

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Background: Tourette’s syndrome (TS) is a developmental neuropsychiatric disorder characterized by multiple motor and vocal tics. Many TS patients substantially improve by early adulthood. It is unknown why some patients with TS remit while others suffer lifelong symptoms. Hypothesized abnormalities in sensory motor gating such as prepulse inhibition (PPI) have been proposed.

Methods: We studied 35 adults (11 active TS, 7 remitted TS, 16 unaffected controls). We used a tactile startle paradigm to measure PPI. A block design with three conditions: pulse-alone; prepulse-pulse (PPI); and rest was used. Eye-blink reflex startle response was measured outside the scanner.

Results: There were no differences among groups in the amplitude or habituation of the startle response. A normal level of PPI was observed in the healthy adults (63.7% reduction), PPI however, was lower in both the remitted (31.2% reduction) and in the active TS (41.9% reduction) groups. After subtracting the mean beta values of the pulse condition from the PPI condition, we identified 9 regions that differed between the TS cases and controls, but not between remitted and active TS cases. In five additional regions, including both the L and R caudate (CN), we observed a significant difference between the remitted and active TS groups. Regression analyses in these regions also demonstrated a significant positive linear relationship (p<0.02) between tic Severity and PPI in both the L CN (r = .50, p = .02) and R CN (r = .45, p = .04).

Conclusions: These findings suggest that reduced PPI is a trait finding in TS.

LATE BREAKING ORAL SESSION

Late Breaking Oral Session

Friday, May 21, 2010 3:00 PM - 5:00 PM

Location: Grand Couteau - 5th Floor

Chair: See Program Book

396.-403. Late Breaking Oral

At time of publication the Late Breaking oral abstracts had not been accepted. Please see the on-line Program Planner at www.sobp.org for the complete abstracts accepted for this session.
404. NIMH Funding: Priorities, Opportunities, and Strategies

Mark Chavez, Thomas Insel, Steven Zalcman

The purpose of this session is to cover select topics about NIMH grant funding that are directly relevant to junior investigators. Dr. Thomas Insel will provide a brief overview of the NIMH strategic plan and current NIMH funding priorities. Drs. Mark Chavez and Steven Zalcman will cover topics focusing on those funding opportunities most pertinent to junior investigators, review criteria specific to research training and career development awards, current NIMH policies directed toward junior investigators, and strategies for transitioning toward research independence. As this session is intended primarily to serve as a platform for open discussion and interaction, there will be ample time for questions and answers. Presenters: Mark Chavez, Ph.D., Associate Director for Research Training & Career Development, Thomas Insel, M.D., Director of NIMH, and Steven Zalcman, M.D. Branch Chief of Clinical Neuroscience and Experimental Therapeutics

405. Obsessive-Compulsive Symptoms Dimensions Among Patients with and without Tics

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Methods: Participants were recruited from a clinical sample of 813 consecutive OCD outpatients from the Brazilian Obsessive-Compulsive Disorder Consortium from 2003 to 2008. Inclusion criterion was: main psychiatric diagnosis of OCD (DSM-IV). Exclusion criterion: comorbid schizophrrenia, mental retardation or any other condition that could impair the understanding of the protocol. All participants provided written informed consent. Instruments applied were: SCID-I, and SCID for Impulse-Control disorders; Y-BOCS, DY-BOCS, YGTSS. There were no self-report assessments. To compare the categorical variables concerning patients with and without tics chi-square tests were performed. To compare the same groups concerning the continuous variables Mann-Whitney non-parametric tests was performed. A significance level of 5% was considered.

Results: 813 OCD patients (338 males, 475 females), of which 236 were OCD patients with tics and 577 had OCD without any tic disorder. Among OCD patients with tics, the mean age of appearance of first tics was 12.11 years (ep=0.549) and the mean severity of tics (YGTSS) was 27.20 (ep=1.418). Despite no differences between group regarding global scores (DY-BOCS), aggressive, sexual/ religious, symmetry and hoarding dimensions scored significantly higher among OCD plus tics group.

Conclusions: Obsessive-compulsive symptoms dimensions have different pattern in OCD plus tics when compared to OCD without tics. The pattern of symptoms dimensions is complementary evidence that OCD plus tics consists a particular group of obsessive-compulsive spectrum disorders.

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406. Searching for a Uniform Factor Structure for PTSD Symptoms: A Six Factor Model

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Background: As the publication of the DSM-V is scheduled for 2012, debate on how PTSD should be defined rises. Several alternative factor-models to the DSM-IV model have been proposed in the last decennia.

Methods: The current study examined the DSM-IV factor structure, and two alternative factor models, which have been frequently confirmed (King et al 1998; Simms et al, 2002). In addition, an alternative six-factor model was developed and explored. Data was collected with the Clinician-Administered PTSD Scale (CAPS) in a sample of male, Dutch military veterans (N = 81).

Results: A nested six-factor model comprising re-experiencing, effortful avoidance, emotional numbing, anhedonia, hostility, and trauma-related amnesia, fitted the data the best. Within the nested factor solution, symptom clusters were divided in a category of either PTSD-specific or other distress symptoms.

Conclusions: Several conclusions were drawn regarding the results, including a comparison with Horowitz’ (1979) conceptualization of PTSD, the ICD-10 criteria for PTSD, and a proposal to revise the symptom clusters of the current PTSD diagnosis.

407. Heritability of Glucose Metabolism in the Rhesus Monkey Brain During Exposure to Potential Threat

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Background: We examined individual differences in brain metabolic responses to a mildly threatening stimulus with positron emission tomography (PET) in a large sample of young rhesus monkeys (n=238; average age = 2.4 years) all belonging to a single-family multigenerational pedigree. The power to estimate heritability in this sample derives from the presence of substantial numbers of closely related, distantly related, and unrelated pairs that all contribute information concerning the effects of kinship (shared genes) on phenotypic similarity.
Methods: Monkeys were injected with fluoro-18-deoxyglucose (FDG) and placed in a test cage for 30 minutes in the presence of a human “intruder” who stood 2.5 meters from the cage making no eye contact (NEC) with the monkey. To examine the heritability of glucose metabolism in response to the NEC challenge, a voxelwise heritability analysis was performed using SOLAR software that controlled for the potential confounds of age, sex and gray matter probability at each voxel.

Results: Brain activity during NEC was significantly heritable in bilateral anterior hippocampal regions (right: h^2=0.66, p=2.8e-05; left: h^2=0.76, p=3.4e-06). No significantly heritable clusters were observed in the amygdala. Furthermore, heritability estimates in the dorsal prefrontal cortex (PFC) and posterior cingulate cortex (PCC) ranged from h^2=0.7 to h^2>0.95, and were highly significant (p<1.0e-5).

Conclusions: These results suggest that threat-related glucose metabolism in anterior hippocampus, the PCC and the PFC reflect inherited neural responses to acute stressors.

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408. Effects of Serotonin Transporter and Tryptophan Hydroxylase-2 Gene Variation on the Response to Cognitive-Behavior Therapy in Individuals with Social Anxiety Disorder

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Background: The short (s) allele of the serotonin transporter linked polymorphic region (5-HTTLPR) and the T variant of the G-703T polymorphism in the tryptophan hydroxylase-2 (TPH2) gene are associated with amygdala hyperresponsivity in patients with social anxiety disorder (SAD). Treatment studies have previously reported poorer response to placebo and insufficient attenuation of amygdala activity in SAD patients carrying the TPH2 T variant, and poorer response to antidepressants in carriers of the 5-HTTLPR s allele. The present study evaluated the effects of these polymorphisms on the response to cognitive-behavior therapy (CBT).

Methods: Participants diagnosed with SAD (N=204, 123 females, mean age 38±11 years) were randomized to Internet-delivered CBT or to a waitlist control. In the CBT group, a significant linear trend interaction (F=4.42, df=1,99, p=.038) supported better improvement in TPH2 GG homozygous individuals (n=59) relative to T carriers (n=42). The 5-HTTLPR polymorphism did not influence treatment outcome and gene-gene interactions were not observed.

Results: Treated individuals improved significantly (p<0.0001) more than controls. In the CBT group, a significant linear trend interaction (F=4.42, df=1,99, p=.038) supported better improvement in TPH2 GG homozygous individuals (n=59) relative to T carriers (n=42). The 5-HTTLPR polymorphism did not influence treatment outcome and gene-gene interactions were not observed.

Conclusions: These results suggest that impaired inhibition of FP s to safety cues is associated with both genetic risk for PTSD and history of childhood maltreatment.

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410. MAO-A and COMT Polymorphisms and OCD: A Brazilian Family-Based Association Study

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Background: There is a complex interaction between serotonin, dopamine, and other neurotransmitters that can influence OCD development. Genes involved in the inactivation of these neurotransmitters, such as Cathecol-O-Methyltransferase (COMT) and Monoamino-oxidase-A (MAO-A) genes, have been associated with psychiatric disorders, including OCD, in genetic studies. Few studies with non-caucasian samples had been performed. This study aims to perform a family-based association study with a Brazilian sample.

Methods: Eight COMT and six MAO-A single nucleotide polymorphisms
(SNPs) were chosen to be analyzed on 73 OCD trios in this study. The genotyping was performed with Sequenom™ and the statistical analysis were performed using Haploview and PLINK.

**Results:** There was no association between COMT and MAO-A and OCD in this sample.

**Conclusions:** These findings do not support an association between COMT or MAO-A genes with OCD. Further studies, with larger independent samples, are still required.

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**411. SLC6A4 Polymorphism is Associated with Treatment Response in Obsessive Compulsive Disorder**


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**Background:** The serotonin transporter (5-HTT), the key modulator of serotonergic neurotransmission, is the target for serotonin reuptake inhibiting drugs (SSRIs), effective in the treatment of obsessive-compulsive disorder (OCD). Family and twin studies suggest a strong genetic component to OCD. However, studies examining the association between OCD and a functional polymorphism in the transcriptional control region of the gene 5-HTTLPR have yielded inconsistent results. This study aimed to identify polymorphisms associated with treatment response in OCD.

**Methods:** 192 outpatients with DSM-IV criteria OCD consented to participate in this study. They were randomly assigned to 12-week treatment with fluoxetine up to 80mg/day or weekly, 2-hour sessions of group cognitive-behavioral therapy. The primary outcome was treatment response at week 12, defined as at least 35% reduction of the baseline Yale-Brown Obsessive Compulsive Scale (YBOCS) score, where the minimum possible score was adjusted to eight points (remission) instead of zero (no symptoms). Twenty-eight single nucleotide polymorphisms (SNPs) involving serotonergic, noradrenergic and dopaminergic systems were investigated among treatment responders and non-responders.

**Results:** 48 out of 123 patients were responders (39%). Among the evaluated SNPs, heterozygosity for the SLC6A4 gene at the rs6355 locus showed an association with a better response (p=0.007).

**Conclusions:** The SLC6A4 gene rs6355 polymorphism, a missense polymorphism that leads to an aminoacid change ALA[G]56GLY[G], has been previously associated with autism and rigid-compulsive behaviors. The results of this study suggest that the polymorphism rs6355 is associated with a positive response to conventional treatments for OCD.

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**412. Genotype-Controlled Analysis of Plasma Dopamine β-Hydroxylase Activity in Civilian Post-Traumatic Stress Disorder**

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**Background:** Norepinephrine (NE) plays a central role in post-traumatic stress disorder (PTSD). Dopamine β-hydroxylase (DBH) converts dopamine (DA) to NE and its activity varies widely across individuals. Mustapic et al. (2007) reported a PTSD-associated deficit in plasma DBH activity (pDBH) in a genotype-controlled analysis of combat veterans. We tested whether such a deficit would occur in a sample of civilians.

**Methods:** The severity of current adult PTSD symptoms and current DSM-IV diagnosis of PTSD were determined by the PTSD Symptom Scale (PSS). Childhood trauma exposure was assessed using the Traumatic Experience Inventory (TEI), pDBH was assayed by HPLC with electrochemical detection and genotypes were determined using the Taqman® platform.

**Results:** Two hundred and twenty seven African American (AA) subjects were enrolled in this study, with a mean age (± SD) of 42.9 (±12.9) years. We found a strong association between rs1611115 genotype and pDBH (p=0.05) in any genotype group. No significant correlations were found between pDBH and PTSD severity, but pDBH significantly associated with the status of comorbid depression based on the cutoff of HAMD (p=0.014) in subjects with PTSD.

**Conclusions:** We have replicated in this sample the prior finding that DBH rs1611115 genotype strongly associates with pDBH. No associations between pDBH and PTSD diagnosis or symptom severity in this civilian sample, but some evidence supports an association between pDBH and depressive symptoms.

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**413. Interaction between FKBP5 Genotype and Stressful Life Events Predicts Threat-Related Amygdala Reactivity in a Community Sample**

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**Background:** The co-chaperone protein FKBP5 influences HPA axis function by modulating GR regulated gene transcription. A common polymorphism in FKBP5 (rs1360780 T allele) has been linked to increased FKBP5 protein levels and cortisol reactivity, as well as risk for psychopathology particularly in interaction with stress. We investigated effects of rs1360780 and the potential moderating role of stressful life events on threat-related amygdala reactivity in 86 healthy, Caucasian volunteers.

**Methods:** FKBP5 genotype was determined using TaqMan® allelic discrimination assay. BOLD fMRI was used to measure threat-related amygdala reactivity. Number of stressful life events was determined from self-report. Gender was entered as a covariate.

**Results:** Stressful life events were not significantly associated with amygdala reactivity (F(1,85)=2.58, p=0.11). While there was no significant main effect

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of genotype (F(1,85)=0.73, p=0.40), there was a significant genotype-by-stress interaction (F(2,84)=5.11, p=0.03). C homozzygotes reporting more than two stressful life events exhibited increased left dorsal amygdala reactivity relative to those reporting two or fewer events. In contrast, amygdala reactivity did not differ as a function of stressful life events in T carriers.

**Conclusions:** Consistent with the critical role of the amygdala in mediating adaptive responses to environmental threat and stress, C homozzygotes exhibited relatively increased amygdala reactivity as a function of stressful life events. In contrast, stressful life events did not influence amygdala reactivity in T carriers. This pattern may be consistent with dysregulated HPA axis function associated with the T allele and could represent a neurobiological pathway for related increased risk of psychopathology in T carriers.

**414. Cortico-Striatal Substance P Release Correlates with Phobia Related Trait Anxiety**

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**Background:** Substance P is a neuropeptide involved in emotional behavior by binding to the NK1-receptor. Regions with high NK1-receptor density in the human brain are the striatum, occipital and frontal cortices as well as the brainstem. Using positron emission tomography (PET), the present study related substance P release to phobic trait anxiety during fear provocation in individuals with specific phobia.

**Methods:** Sixteen adult women with DSM-IV-defined specific phobia for either snakes or spiders viewed phobic and non-phobic pictures while in a PET-scanner. The highly specific NK1-receptor antagonist ([11]C)GR205171 was used as tracer during the PET-assessments. Substance P release was indexed by the difference in NK1-receptor occupancy during phobic and non-phobic stimulation.

**Results:** The difference in ([11]C)GR205171 uptake between the phobic and non-phobic conditions correlated negatively with specific phobia trait during fear provocation in individuals with specific phobia.

**Conclusions:** High trait anxiety is associated with high substance P release during phobic fear. This might suggest a role for substance P in persistent avoidance behaviors.

Supported by Swedish Research Council

**415. Differences in Fear Circuit Connectivity between Responders and Non-Responders to SSRI Treatment of Social Anxiety Disorder - A Bayesian Approach**

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**Background:** The aim of the present study was to characterize effective brain connectivity patterns in responders and non-responders to treatment with SSRI in patients with social anxiety disorder (SAD).

**Methods:** Patients with SAD were treated with SSRI and classified into responders or non-responders by the Clinical Global Impression improvement item (CGI-I). A public speaking task was performed by 33 patients after 8 weeks of treatment. During the speech regional cerebral blood flow (rCBF) was measured using [15O]-labelled water and positron emission tomography. Different connectivity architectures were built based on five regions of interest (ROIs): the amygdala, subgenual anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), insular cortex and brainstem. Structural equations modelling and Bayesian inference were used to assign probabilities to all possible architectures.

**Results:** Top ranking models reveal different connectivity patterns in responders and non-responders. In non-responders the brainstem drives the OFC and the amygdala influences the insula. In responders the OFC, and not the amygdala, drives the insula. Also, there is weakened or no influence from the brainstem to the OFC in responders.

**Conclusions:** These results suggest that bottom-up processes from the brainstem and the amygdala that are present in the SSRI non-responders are absent and replaced with top-down processes from the OFC in the SSRI responders.

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**416. Neural Effects of Pregabalin in Healthy Controls during Anticipation**

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**Background:** fMRI has potential as a bioassay for development of novel anxiolytics, which would be Supported by common findings across drug classes. Benzodiazepine and SSRI treatment have been found to reduce activity in bilateral amygdala and insula during emotional-processing tasks. Pregabalin (PGB) is a novel anxiolytic that binds to α2-δ subunits of N- and P/Q-type Ca2+ channels. The current fMRI study sought to elucidate neural mechanisms for anxiolytic effects of PGB.

**Methods:** For this double-blind crossover-design study, 16 healthy controls (6 Female) completed three fMRI scans, conducted 60 minutes after placebo, 50mg, or 200mg PGB administration. The fMRI paradigm involved cued anticipation of positive- (PA) and negative- (NA) valenced images. Linear mixed effects analysis was implemented in R; results were constrained to regions of interest (anterior insula, amygdala) using AFNI. Significance was defined at p<0.05, with Monte-Carlo adjustment for multiple comparisons.

**Results:** Dose-response effects (decreased activation for both NA and PA) were found for right anterior insula and left posterior amygdala. Dose-response by valence effects (increased activation for NA, decreased for PA) were found for right anterior insula and left anterior amygdala.

**Conclusions:** Pregabalin, similar to benzodiazepines, may influence activation
417. Impact of Cerebellar Volume in PTSD
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Background: The cerebellum might play a role in anxiety manifestations like hyperarousal symptoms, which are present in different disorders such as posttraumatic stress disorder (PTSD) and generalized anxiety disorder (GAD). Recent evidence suggests that cerebellum may be involved in PTSD, reported as smaller cerebellar volume (both hemispheres) in children secondary to maltreatment and supplementary motor cortex activation in response to traumatic reminders.

Methods: Thirty seven healthy controls and fifty two subjects with posttraumatic stress disorder (PTSD) who had ICD-10 criteria, matched for gender, age, and years of education, were submitted to psychometric (by CAPS and ETI scale) and resonance magnetic image evaluation.

Results: Unadjusted means of right cerebellum hemisphere (F=5.053, p=0.027), vermis (F=31.766, p=0.001) and cerebrum (F=16.093, p=0.001) were smaller in the PTSD group. But the group differences remained significant in the right cerebellum (F=8.056, p=0.004) and vermis (F=11.125, p=0.001) in the analyses adjusted for cerebral volume, gender, age and schooling. Cerebellar vermis (B=-6.566, t=-3.438, p=0.001) and cerebrum (B=-1.063, t=-1.414, p=0.016) volumes negatively correlated with Clinician-Administered PTSD Scale (CAPS). Cerebellar vermis volume (B=-10.492, t=-1.487, p=0.014) negatively correlated with Early Trauma Inventory (ETI).

Conclusions: Vermis and right cerebellar hemisphere might be reduced in subjects in PTSD. Future follow-up studies examining larger samples are warranted to validate these preliminary findings.

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418. Parsing the Effect of Anxiety Domains on Limbic Responses to Face Processing
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Background: Anxiety-prone individuals show hyperactivity in limbic regions during emotional face processing. However, less is known about the contributions of different domains of anxiety. This study aimed to delineate the contributions of social anxiety, trait anxiety, and anxiety sensitivity on limbic activation during emotional face processing.

Methods: Ninety-nine young adults were tested on an emotional face processing task (Hariri et al., 2002) during fMRI (51 participants at 1.5T, 48 at 3T). Participants also completed the Social Interactional Anxiety Scale (SIAS), Spielberger Trait Anxiety Inventory (STAI), and Anxiety Sensitivity Index (ASI). Using a robust multiple regression approach implemented in R, with magnet as a covariate, we examined the effects of social anxiety (SIAS), trait anxiety (STAI), and anxiety sensitivity (ASI) on limbic activation to emotional faces. To obtain unbiased estimates, t-statistics were computed using a bootstrap estimate of each partial regression coefficient’s standard error.

Results: SIAS, STAI and ASI were correlated significantly (rs=.44-.58). Using a volume and t-thresholded cluster approach with constrained regions of interest, we found that, adjusting for all other variables, social anxiety was associated with activity in dorsal anterior cingulate and right amygdala, and inversely associated with activity in right posterior insula.

Conclusions: Although hyperactivity in amygdala and anterior cingulate have previously been associated with high anxiety in general, the current findings are consistent with the hypothesis that limbic hyperactivity during emotional face processing is primarily due to social anxiety. Thus, emotional face processing tasks may not be optimal for assessing other types of anxiety.

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419. Amygdala Response to Familiar, Not Novel, Faces Characters Influences Inhibited Temperament
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Background: Inhibited temperament increases risk for social anxiety and major depression. The magnitude of the amygdala’s response to novelty has been identified as a possible neural substrate of inhibited temperament; however, prior studies have also reported large responses to familiar faces. In this study, we increased the familiarity of the faces and increased the sample size.

Methods: Participants had inhibited (n=18) or uninhibited temperament (n=15). We performed a slow event-related fMRI (3T) study to measure the amygdala’s response to both novel and familiar neural faces. We used SPM5 to identify significant clusters (p < .05, cluster > 12) of activation, extracted the average percent signal, and performed post-hoc ANOVAs to confirm the findings.

Results: Both left and right amygdala showed significant interaction of Temperament Group X Face Type (both ps < .05). For the uninhibited group, amygdala response to the novel faces was greater than the response to the familiar faces, with a baseline response to familiar faces. In the inhibited group, amygdala response was high for both the familiar and novel faces.

Conclusions: These findings suggest that response to familiar faces may be as or more important than response to novel faces in inhibited temperament. The continued amygdala response to familiar faces in inhibited subjects likely underlies developmental risk for social anxiety and may reflect either a slower habituation to faces or a failure to consider even relatively familiar faces to be safe.

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420. Expectancy and Surprise Influence Attention to Emotional Information
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Background: Threatening stimuli capture attention particularly when unexpected. This implies the existence of a neural system which tracks threat expectancy and deploys attention accordingly. We assessed whether a Bayesian learning computational model (BLM), analogous to the Rescorla-Wagner model used to track reward expectation, predicted both behavioural and neuroimaging measures of attention to threat. We also assessed whether trait anxiety was associated with the use of expectancy to control attention to threat.

Methods: During fMRI scanning, 29 healthy volunteers completed a task which varied the frequency of threatening stimuli. Trait anxiety was measured
prior to scanning. For each individual a trial-by-trial estimate of threat expectation and surprise was obtained from the BLM. These derived signals were then regressed against reaction time and BOLD response to provide estimates of the ability of the model to explain behavioural and neuroimaging measures of attention.

**Results:** Attention, as indexed by speed of response and visual cortex activity, was increased when a stimulus was expected to be threatening. The expectancy signal was also observed in OFC and right amygdala suggesting a possible role for these areas in generating the signal. Surprisal was associated with activity in both visual cortex and ACC. A higher trait anxiety was associated with decreased expectancy signal in both amygdala and subcallosal ACC.

**Conclusions:** A network of areas including OFC, the amygdala and ACC are involved in tracking the expectation of threat and deploying attention accordingly. The attentional control difficulties associated with anxiety may result from suboptimal use of this system. Supported by Wellcome Trust WT081672MA

**421. Cortical Thickness Analysis of Individuals Exposed to Trauma**

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**Background:** Posttraumatic Stress Disorder (PTSD) has been associated with various structural abnormalities in various regions of the brain, specifically in the medial frontal areas. It has been hypothesized that smaller cortices may contribute to the inability of patients to remit from the initial symptoms. However, no studies so far have investigated, in a longitudinal design, the relationship between cortical thickness and PTSD severity symptoms.

**Methods:** 42 trauma-exposed and 27 healthy control subjects received a high-resolution structural magnetic resonance imaging (MRI) scan of the cerebrum at the Montreal Neurological Institute (MNI), and were assessed for clinical status by a trained psychologist. Cortical thickness was assessed at over 40,000 using the CIVET pipeline software of the MNI. Multiple Regression analysis was then employed to establish associations between PTSD symptom severity and cortical thickness.

**Results:** Significant associations between cortical thickness and symptom severity of PTSD were observed in the right frontopolar (BA10; t=5.11, p<.05), right occipitotemporal gyrus (BA 20; t=-4.31, p<.05), and the left occipital gyrus (BA 18; t=-3.77, p<.05) across the entire group of PTSD exposed subjects.

**Conclusions:** The current results suggest that specific areas in the brain involved with visual processing and cognitive branching might be positively and negatively associated with symptom severity in PTSD. These contrasting effects can be used to formulate a model where specific structures in the brain serve as either vulnerability or resilience factors for the development of PTSD after trauma. Supported by Canadian Institute of Health Research

**422. DTI Studies of Pediatric Maltreatment Related PTSD**

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**Background:** To examine the corpus callosum microstructure of maltreated related PTSD to that of maltreated and non-maltreated controls.

**Methods:** We compared anatomical brain measures of maltreated children with PTSD (n=50), maltreated children without PTSD (n=46), and non-maltreated controls (n=105) on measures of FA values using Diffusion Tensor Imaging (DTI) at 3 Tesla. Maltreatment groups were similar most variables. Sexual abuse was more common in PTSD group.

**Results:** We found that FA values were lower in most CC regions of maltreated children without PTSD compared to maltreated children with PTSD. FA values were higher in children with PTSD in the genu, midbody and isthmus subregions of the corpus callosum. These data strongly suggest that our previous findings of adverse brain development in maltreated children with PTSD may be related to having PTSD in childhood and not maltreatment experiences per se. We found the expected posterior regional increases of FA with corpus callosum regional areas in maltreated children without PTSD. However, no relationships were seen with age and FA values in maltreated children with PTSD. There were significant group by age interactions for posterior midbody (group x age interaction t=-2.68 p=.009) and splenium (group x age interaction t=-2.16, p<.03), and a trend for isthmus.

**Conclusions:** These data suggest that microstructural myelination differences are associated with resilience to PTSD. Neurobiological resilience cannot assume to mean no anatomic brain differences from non-maltreated children, but rather a neuroalteration that may be responsible for resilience and another type of dysregulation that may be responsible for PTSD. Supported by K24MH71434, MH61744, MH63407

**423. Regional Cortical Thickness and Gray Matter Volume as Predictors of Recovery from Post-Traumatic Stress Disorder**

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**Background:** Decreased cortical thickness in frontal and temporal regions has been observed when comparing patients with Post-Traumatic Stress Disorder (PTSD) to controls. In addition, it has been recently shown that decreased gray matter volume in the rostral anterior cingular cortex (ACC) predicted poorer outcome in a small sample of PTSD patients.

**Methods:** Thirty-one patients suffering from moderate to severe PTSD were scanned following an initial clinical assessment. Symptom improvement, indexed by the change in CAPS scores 6-9 months later, was regressed against two measures of cortical structure: 1) gray matter volume, determined using Voxel Based Morphometry and 2) vertex-based cortical thickness.

**Results:** Symptom improvement was predicted by both increased gray matter volume and cortical thickness in the subgenual ACC. Cortical thickness was also a positive predictor of symptom improvement in the dorsal ACC, the lateral prefrontal cortex and the precuneus. Interestingly, decreased cortical thickness in a more anterior region of the ventral medial prefrontal cortex (vmPFC) was associated with stronger symptom severity at the first assessment.

**Conclusions:** Conclusions: Our results confirm and extend previous reports of an association between ACC structure and recovery potential. In addition, these findings suggest that different areas within the vmPFC may be dissociable in terms of their relationship with PTSD symptom manifestation and recovery potential. Supported by CIHR, FRSQ, CPRF, NSERC
424. Neuroroticism Modulates the Impact of Anticipatory Anxiety on Experiential, Autonomic, and Neural Responses

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Background: Neuroroticism is a known risk factor for anxiety disorders. Prior findings suggest that neuroroticism is related to increased responding to aversive stimuli, but it is not clear whether neuroroticism affects anticipatory responding. Given that many anxiety disorders are characterized by chronic worry and anxiety about the future, it seems possible that neuroroticism is related to these anticipatory responses.

Methods: We designed a paradigm in which electric shocks were threatened and delivered to the wrist at variable intervals and intensities (safe, medium, strong). This permitted investigation of a dynamic range of anticipatory anxiety responses. In two studies, 96 and 55 healthy female participants respectively underwent the shock anticipation paradigm while providing continuous ratings of anxiety experience and electrodermal responding (Study 1) and during fMRI scanning (Study 2).

Results: Results indicated that individuals high in neuroroticism reported greater anxiety and exhibited greater skin conductance responses across all three task conditions. Study 2 revealed an interaction between neuroroticism and task condition. Compared to low neuroroticism participants, high neuroroticism participants displayed a steeper increase in neural responses from safe to medium to strong trials in the medial frontal gyrus, middle frontal gyrus, anterior cingulate cortex, and putamen.

Conclusions: Findings suggest that individual differences in neuroroticism influence sensitivity to anticipatory threat. These findings provide new insights into the mechanism through which neuroroticism may confer risk for developing anxiety disorders via elevated and sustained anticipatory responses. Supported by NRSAD 1104076-100-UACKV

425. Alexithymia and Early Emotional Neglect: The Creation of Alexithymia Subtypes

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Background: Alexithymia is a personality trait associated with difficulties in identifying, decoding and communicating personal feelings. In addition, it has shown to be a risk factor for affective disorders. Recent studies have underlined the need to differentiate the construct of alexithymia, however, current subtype models lack empirical support. We propose that the consideration of trauma dimensions and fMRI may be capable of revealing distinct subtypes of alexithymia. Results of both a psychometric and a neurobiological differentiation are reported.

Methods: Alexithymia and childhood trauma were investigated in a high alexithymic but psychiatrically healthy community sample (N=50) in comparison with a non-alexithymic healthy sample (N=50). Alexithymia was assessed using the Toronto-Alexithymia-Scale (TAS-20) and the Bermond Vorst Alexithymia Questionnaire (BVAQ). Early traumatic experiences were measured by the Childhood Trauma Questionnaire (CTQ) and the Early Trauma Inventory (ETI). Neural correlates of emotion processing were investigated by the fMRI paradigm using pictures of emotional expressive faces and emotional music clips to induce fear and happiness in the subjects.

Results: There was a significant correlation between alexithymia and early emotional neglect as well as a higher level of early emotional neglect in the high alexithymic sample compared to controls. Within the high alexithymic group, early emotional neglect predicted the overall level of alexithymia and the score on two alexithymia facets. fMRI revealed different neural activation patterns in response to happiness and fear inducing stimuli as a function of alexithymia and early emotional neglect.

Conclusions: Early emotional neglect seems to be a suitable variable to differentiate between alexithymia subtypes. This is true on both a psychometric and a neurobiological level. Supported by German Research Foundation

426. Heightened Amygdala and Hippocampal Responsivity to Emotional Faces in Youth with Posttraumatic Stress Disorder Symptoms: An fMRI Study

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Background: Youth with posttraumatic symptoms demonstrate attention bias away from threatening faces (1,2). Functional neuroimaging has demonstrated enhanced amygdala response in adults with PTSD when processing fearful expressions (3, 4). Since our laboratory has identified limbic abnormalities in youth with PTSS (5), we examined brain regional differences when processing facial expressions.

Methods: 46 right-handed, medication naïve youth (23 with PTSS and 23 healthy controls) underwent clinical (CAPS-CA, WASI) and neuroimaging assessment in a 3T MRI scanner. Experimental task: 24 second blocks (8 faces at 3 sec/face) of each facial expression: angry, fearful, happy, sad, and neutral and scrambled. Data were analyzed in SPM5 using a 3-way ANOVA of group x face x phase; where phase equals early or late half of each block. Significant activation from group x phase were extracted using MARSBAR, and analyzed in SPSS.

Results: The CAPS-CA mean score was 38.9 (17.0). Significant activation was found in the right amygdala, right and left hippocampus, right insula, left orbital, left thalamus, right visual cortex and right postcentral gyrus. Exported to SPSS, these regions showed group differences. Angry faces: PTSS>HC in the right amygdala and left hippocampus - early phase, Sad faces: PTSS>HC in the right amygdala - early phase. Neutral faces: PTSS>HC in the left thalamus - early phase. Fear faces: HC>PTSS in the right visual cortex - late phase.

Conclusions: As suggested by Whalen and colleagues, amygdala responsivity may be part of a “constant vigilance system” responding to ambiguous stimuli. This normal mechanism may be sensitized in youth with PTSS. Supported by NIMH63893; NARSAD; AFSP

427. fMRI of Maternal Attachment and the Contribution of Preoccupied Attachment Style to Neuronal Activation

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Background: Attachment style -- the ability to adaptively reflect upon the thoughts, feelings or memories associated with attachment relationships, has
been shown to influence the efficacy of individual psychotherapy in depression (McBride et al, 2006). The neurobiological mechanisms subsuming this influence and their relationship to depression are unknown. To this end we employed fMRI to study neural representation of attachment in depressed and healthy young females.

**Methods:** 20-30 year old females with no psychopathology completed assessments including the Relationship Style Questionnaire (RSQ). Subjects viewed photos of their mother, a close friend and age matched strangers (old and young). Contrasts compared mother to others and the preoccupied attachment score was entered as a covariate. Images were acquired using a Siemens 3T scanner (TR=2s, slice thickness=3mm) and analyzed using SPM8.

**Results:** For the mother versus others contrast activation was seen extensively in the occipital cortex, lingual gyrus, and bilateral thalamus. Activation was also seen bilaterally in the anterior cingulate. Deactivation was seen in the bilateral insula and precentral gyrus. Preoccupied attachment style contributed to neuronal response to mother versus others with areas of activation in the occipital cortex and bilateral thalamus, bilateral anterior cingulate and bilateral insula.

**Conclusions:** In healthy control subjects, viewing the mother is associated with unique patterns of activation with substantial contributions correlated with measures of preoccupied attachment. Supported by Hope for Depression Research Foundation

**428. CANDIShare and the Internet Brain Volume Database: Resources for Pediatric Neuroimaging Data**

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**Background:** There are numerous psychiatric disorders that can plague the development of children. In the area of neuroimaging, a substantial number of studies have been performed to date; and while much has been learned from these assessments including the Relationship Style Questionnaire (RSQ). Subjects viewed photos of their mother, a close friend and age matched strangers (old and young). Contrasts compared mother to others and the preoccupied attachment score was entered as a covariate. Images were acquired using a Siemens 3T scanner (TR=2s, slice thickness=3mm) and analyzed using SPM8.

**Results:** For the mother versus others contrast activation was seen extensively in the occipital cortex, lingual gyrus, and bilateral thalamus. Activation was also seen bilaterally in the anterior cingulate. Deactivation was seen in the bilateral insula and precentral gyrus. Preoccupied attachment style contributed to neuronal response to mother versus others with areas of activation in the occipital cortex and bilateral thalamus, bilateral anterior cingulate and bilateral insula.

**Conclusions:** The sharing of data is most effective when shared in a way that preserves the linkages between the images, the resultant analytic data and meta-data, and it’s relationships to other public sources of related information. This represents a ‘Knowledge Management’ environment that will facilitate traversal of these data and linkages in support of pediatric neuroimaging studies.

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**429. A Multi-Voxel in Vivo 31P Spectroscopy Study at 4 Tesla in Healthy Children and Adolescents**

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**Background:** The high prevalence of the onset of many psychiatric disorders during childhood and adolescence highlights the importance of understanding the molecular biochemistry of healthy neurodevelopmental trajectories in the maturing brain. In vivo 31P spectroscopy is a powerful non-invasive technique that shown promise in detecting biochemical changes in the developing brain at 1.5 Tesla by the measurement of precursor and breakdown product levels of membrane phospholipids (MPLs) i.e., [phosphoethanolamine (PE) and phosphocholine (PC), and glycerophospho-ethanolamine (GPE) and glycerophosphocholine (GPC)]. The structural wall separating the various cellular entities such as the branching of dendrites and synaptic connections is composed of MPLs in a bilayer conformation. Early in postnatal brain development of animals, PE levels are high, and GPC and GPE levels are low reflecting the high demand of MPL synthesis for the development of cell membrane structures required in dendritic and synaptic connections. As the brain develops, PE levels decrease, and GPC and GPE levels increase with age. In the context of rapid proliferating tissue, elevated levels of MPL precursor levels, specifically PC, have been observed at the time and site of neuritic sprouting in the hippocampus following unilateral lesions of the entorhinal cortex in rats. The purpose of this study is to investigate changes in MPL metabolites of healthy children and adolescents to discern developmental growth spurts in cortical and subcortical structures using in vivo 31P spectroscopy at a higher magnetic field strength.

**Methods:** PE, PC, GPC, and GPE levels were quantified bilaterally in the DLPFC, dorsal anterior cingulate (dACC), striatum and superior parietal lobe (sPL) of 23 healthy control (HC) children and adolescents (9M+14F; mean age 11.3±3.7 yrs; 6.2 to 17.9 years in age range) using a 3D whole-brain, multi-voxel in vivo 31P spectroscopy acquisition method at 4 Tesla. Though cross-sectional, metabolite levels were modeled using either a linear or quadratic function based on significance.

**Results:** PE levels significantly decreased with age linearly in prefrontal and striatal areas [DLPFC: r= -0.671 (p<0.0001); dACC: r= -0.392 (p=0.009)]; striatum: r= -0.686 (p<0.0001); the PE-age association in the sPL failed to reach significance [r=−0.318 (p=0.055)]. The quadratic term also was significant for PE in the dACC (p=0.0067). Regarding the trajectory of PC levels with age, the behavior was quadratic in prefrontal cortices [DLPFC; peaked at ~10.5yrs (p=0.044); dACC: peak at ~10yrs (p= 0.0038)] but not in the striatum or sPL.
GPE levels significantly increased with age linearly in the DLPFC (r= 0.393; p= 0.0044) and dACC (r=0.365; p= 0.0049).

Conclusions: The decreasing PE levels with age appear to reflect a possible reduction in the demand MPL synthesis of neuronal and synaptic processes. In contrast, the inverted “U” behavior in PC levels with age in prefrontal cortices appears to reflect growth spurts in these later developing brain areas. During a growth spurt, which involves the branching out of dendrites and the formation of new synapses in the neuropil, one would expect increased MPL precursor levels of PC reflecting this increased proliferation of cortical tissue. The cross sectional nature of this study warrants appropriate caution in interpreting the results. Nevertheless, they provide an exciting possibility in investigating the molecular biochemistry of temporal trajectories in healthy development and psychiatric disorders in appropriately designed longitudinal studies.

Supported by Children Research Center of Michigan; NARSAD

430. Increased Cerebral Blood Flow in White Matter of Females with Familial History of Depression

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Background: Familial history and gender influence occurrence of depression (MDD) and are associated with differing neural circuitry. However, pre-diagnosis neurophysiologic alterations are not known. Imaging studies with offspring of adults with MDD (FH+) have been inconclusive. Few functional imaging studies in children with mood disorders exist and none are in asymptomatic FH+. Here, we used pulsed arterial spin labeling (PASL) MRI to determine FH+ and gender influences on regional cerebral blood flow (CBF) in non-depressed adolescents.

Methods: Adolescents without mood disorder (n=288, 11.7-15.8 years, 146 females, 139 FH+, 149 FH-) participated in this study. PASL-MRI scans were submitted to voxel-wise analysis to determine differing resting CBF patterns. Once regions of interest were identified, meta-analytic connectivity modeling (MACM) was performed to establish their functional connectivity.

Results: The FH+ group had increased CBF in extra-nuclear, cingulate, and sub-gyral frontal white matter. These regional differences were attributed to the FH+ females (Figure 1). The MACM showed strong functional connectivity amongst these regions (Figure 2).

Conclusions: Increased CBF white matter was seen in FH+ non-depressed adolescents. This pattern was seen to a greater extent in FH+ females, suggesting it may contribute to vulnerability of females in adolescence and puberty to depression. The MACM confirmed that these white matter regions join functionally-related cortical areas, including the dorsal cingulated and prefrontal regions implicated in adult depression. We propose that increased blood flow to these white matter regions corresponds to processes (e.g., inflammation) that later result in apoptosis or necrosis of oligodendrocytes reported in MDD.

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431. Atlas-Based Analysis and Visualization of Diffusion Properties in Group Studies with Linear Regression Model Over Time

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Background: Focus on primates in neuroimaging has increased, as pathological and environmental exposures can be studied in well-controlled settings. Understanding the normal developmental trajectory of the brain in primates will be important for interpreting findings from experimental studies currently in translational research.

Methods: Structural and diffusion-weighted MR (DTI) images (3T) were acquired, and diffusion properties were calculated for twenty-four healthy rhesus monkeys (male and female; 10-72 months old) including fractional anisotropy (FA) and mean diffusivity (MD). Co-registered ROIs in all subjects were generated using an automatic atlas-based brain segmentation. Brain development rates were computed in different lobar parcellations of white matter (WM) and gray matter (GM) respectively. A linear regression model of FA and MD over age was constructed for comparison across different subjects, across different lobes and between regions for WM and GM.

Results: We observed a well-fitted linear regression model for FA and MD. Over time, FA values increase while MD values decrease for both WM and GM. We hypothesize that the MD change is mostly associated with myelination, while the FA change could be caused by the local reorganization and possibly synaptic pruning in regions close to the WM/GM boundary. We also discovered that the developmental change in both FA and MD are highly correlated between WM and GM in corresponding regions.

Conclusions: The results demonstrate a strong age dependence of DTI measurements in WM and GM, and furthermore, the inter-subject variability is smaller than longitudinal or cross-lobe change.

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432. Emotion Circuits in the Parental Brain Vary with Gender, Correlate with Mood, and Predict Behavior

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Background: Parenting requires social cognitive and affective circuits to regulate thoughts and behaviors for reciprocal interactions with their infants that contribute to infant development. We hypothesized that discrete parental
brain regions, differing from non-parents, respond to baby-stimuli modulate mood-regulation circuits and predict infant-directed parental behavior.

**Methods:** We scanned and interviewed non-mothers (n=10), non-fathers (n=10) as well as mothers (n=18) and fathers (n=16) at 2-4 weeks and 3-4 months postpartum. At each time point, fMRI scans assessed brain activity while attending to their own baby-cities pictures. In addition to interviews, parent-infant interaction video-tapes were assessed at 4 months postpartum.

**Results:** Newest analyses replicate parental brain-response findings in emotion regulation circuits and focus on comparisons with non-parents, gender differences and correlations. Cortical responses were markedly increased in parents compared to non-parents. First-time parents activate more in mothers than fathers at 2-4 weeks, but over 3 months, alarm responses in mothers shift to hypothalamus (metabolic control), nucleus accumbens (reward), and frontal cortical (planning) activations as the parent-infant bond develops. Psychometric data indicate significantly higher preoccupations in moms compared to dads (p<0.001), and correlations of pre-occupations with depression (p<0.001), and brain activity in the amygdala and basal ganglia (fear, worry, and OCD circuits) with anxiety and frontal circuits with depression at 2 weeks; brain activity in amygdala predicts parental sensitivity 3 months later.

**Conclusions:** Parental brains respond to baby stimuli vary with gender and correlate with concurrent mood and later behavior linking parental brain function with behavior and offspring outcome.

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### 433. Social Subordination Stress and Serotonin Transporter Genotype Influence Emotional and Physical Development in Juvenile Female Monkeys

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**Background:** Social subordination in macaque adult females produces a dysregulation of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis and is associated with adverse health outcomes that are influenced by polymorphisms in the gene encoding the serotonin transporter (5HTT, SLC6A4). Socially subordinate adolescent females show delayed puberty that is exacerbated by the short (s-variant) promoter length variant in the 5HTT gene.

**Methods:** Because puberty-induced increases in estradiol may be important for continued brain maturation and emotional development in girls, we are using a rhesus monkey model to assess how psychosocial stress during this transition interacts with 5HTT polymorphisms to influence maturation of cortico-limbic serotonin systems and behavior. The present study focused on the pre-pubertal interval (11-22 months of age) in juvenile females from different dominance ranks and with different genotypes to determine if social status-genotype differences emerge prior to puberty.

**Results:** Status did not affect body weight gain. S-variant females initially were heavier than l/l females but grew more slowly than l/l females. A dexamethasone suppression test administered at -18 mo showed no effect of status or genotype, suggesting the LHPA dysregulation seen in subordinates emerges at a later age. Subordinate s-variant females exhibited increased emotional reactivity to threatening novel objects than their counterparts. PET neuroimaging showed no status or genotype differences in 5HTT binding potential in the hippocampus, anterior cingulate, and dorsolateral prefrontal cortex.

**Conclusions:** We will continue to look at substructures of the brain, including the amygdala, to determine whether differences in 5HTT binding could account for this increased emotionally reactivity.

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### 434. Gender Differences in Autonomic Arousal in Adolescence

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**Background:** In adolescence, gender differences have been observed in the rates of mood and anxiety disorders, with females exhibiting higher rates of internalizing disorders. Studies of emotional processes, and specifically autonomic activity, in healthy development can inform our understanding of gender differences in adolescent psychopathology. Few studies have investigated possible influences gender has on autonomic activity in healthy adolescents and, of those few studies, results are conflicting.

**Methods:** Healthy male (n=12) and female (n=12) adolescents completed a reflexive cognitive task (visually guided saccade) while they heard unpredictable (UP) tones that elicited arousal. Autonomic nervous system activity was quantified with cardiovascular measures that differentially measured sympathetic (pre-ejection period) and parasympathetic activity (respiratory sinus arrhythmia).

**Results:** Pre-ejection period length did not differ in male and female adolescents (F(1, 23) = 1.43, p = 0.244), indicating no differences in sympathetic activity. Respiratory sinus arrhythmia was significantly lower in females (F(1,20) = 4.54, p = 0.045), indicating lower levels of parasympathetic nervous system activity in this group.

**Conclusions:** There were no gender differences in emotional reactivity. However, results suggest that in adolescence, emotion regulation systems are less mature in females than in males. Limited vagal tone has been linked to mood and anxiety disorders in adolescence. These results suggest that sex differences in emotion regulation may contribute to sex differences in the rates of mood and anxiety disorders in adolescence.

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### 435. Gender Differences in Healthy Controls in the Default Mode Network

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**Background:** The default mode network (DMN) is a baseline state of brain function accounting for approximately 80% of brain energy use, that is unconfounded by overt behavioral differences and diminished during goal-related tasks. The DMN is hypothesized to be involved in self-referential processes and differences have been seen between varied patient populations and healthy controls but no observations have been made to determine if there are inherent sex differences in the DMN.

**Methods:** The study used 71 healthy men and 76 healthy women matched on age and ethnicity. Subjects were MRI scanned at 3T while they rested quietly and fixated on a crosshair. The DMN was extracted via Independent component analysis (ICA). The DMN signal modulation was further analyzed using a one-way ANOVA in SPM2. A Functional Network Connectivity (FNC) analysis was also run to determine if the DMN was temporally correlated to other “resting state networks” assessed through ICA.

**Results:** The results of the analysis revealed no significant spatial differences in the DMN component activations between males and females. Using FNC analysis, significant (p < 0.05 corrected) but weak sex differences were seen in two network combinations involving (a) the cerebellum, superior parietal-visual cortex, and (b) the posterior cingulate-precuneus/cuneus-lingual gyrus, but none that included connections to the DMN itself.
Conclusions: Overall, any sex differences that emerged are insufficient to make any substantial claim that activation in the default mode is sexually dimorphic.

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436. Interferon-Alpha Treatment In Rhesus Macque; The Behavioral, Biochemical and Hematological Effects of Four Weeks of Daily Treatments

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Background: The cancer-treatment drug Interferon-alpha (IFN-alpha) produces a depressive-like syndrome in humans and animals including non-human primates. Disturbances in the diurnal activity pattern as well as plasma cortisol and measures of anhedonia have also been associated with depression in humans and non-human primates with adverse rearing histories (a potential model of risk for depression).

Methods: Adult monkeys were treated with human recombinant IFN-alpha (20 MU/m\(^2\), S.C.) for four weeks (5 days/wk; a dose previously associated with depressive symptoms). We examined behavioral processes altered in putative animal models of depression: diurnal activity and anhedonia (aspartame preference). Diurnal activity patterns were determined using an automated activity recording system. Aspartame preference compared consumption of sweetened vs unsweetened water in repeated daily tests. In addition to behavioral tests we measured plasma cortisol and IFN-alpha levels and white blood cell counts before and during treatment.

Results: Preliminary findings suggest that IFN-alpha administration disturbs diurnal patterns and aspartame preference during the first week of treatment. In particular, total motor activity was decreased during the first week of treatment but also appeared to recover by week 4. Total fluid volume consumed also appeared to decrease during IFN-alpha treatment though aspartame preference appeared to increase, similar to previous findings following adverse rearing experience in monkeys.

Conclusions: Our preliminary behavioral results appear consistent with previous alterations found in monkeys with adverse rearing history and may provide further insight into the causes and treatment of depressive-like symptoms associated with IFN-a treatment.

437. CRP and Depression: A Test of Alternative Hypotheses

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Background: A substantial research base supports an association between depression and the inflammation marker C-reactive protein (CRP). The goal of the current study is to test two potential confounders - BMI and recent negative events - and two aspects of depression - age of onset and number of depressive episodes - that may account for this effect.

Methods: Three cohorts of children ages 9, 11, and 13 (\(1420\) total) from 11 counties in a rural area of the southeast United States were assessed for psychiatric status annually to age 16 then again at ages 19, 21 and 25 (\(9625\) total observations). Bloodspots were collected from subjects at each wave and assayed for CRP.

Results: Depression status was associated with CRP levels (OR=1.7 95% CI: 1.2, 2.4, \(p<.006\)) and this effect was stronger in males than females. Neither BMI nor exposure to recent negative events mediated the CRP-depression association. Both aspects of depression, however, affected the strength of the CRP-depression association. Prepubertal- and adolescent-onset depression were associated with higher levels of CRP (OR=1.4 95% CI: 1.0, 1.9, \(p<.03\) and OR=1.3 95% CI: 1.0, 1.7, \(p=.02\), respectively), but those with adult-onset depression did not differ from those with no history of depression (OR=1.1 95% CI: 0.7, 1.5, \(p=.78\)). Furthermore, more depressive episodes predicted higher levels of CRP (OR 1.4 95% CI 1.2, 1.6, \(p<.001\)).

Conclusions: The association between depression and CRP levels was robust. The highest CRP levels were observed for those with early-onset of depression and multiple depression episodes.

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438. Reduced Fertility and Fecundity among Patients with Bipolar I Disorder and Schizophrenia in Egypt

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Background: To evaluate procreation among patients with bipolar I disorder (BPI) and Schizophrenia (SZ) in Egypt.

Methods: BPI and SZ patients (N=114 and 79, DSM-IV) were compared with controls (n=124). Fertility was estimated from the proportion of individuals with children. Fecundity was estimated using the average number of children per patient (Total Reproduction Rate, TRR); and marital fertility, the average number of children among patients with conjugal relationships.

Results: The frequency of marriages among BPI patients was higher than SZ group and was significantly lower than the control group (32.5%, 27.8% and 57.3% respectively). Patients with BPI and SZ tend to be childless than controls (16.8%, 17.5% and 46.8% respectively) (BPI: \(\chi^2=24.2, p=8.8e-7\); SZ: \(\chi^2=18.24, p=2.15e-5\)). The TRR for BPI (0.40±1) and SZ (0.32±0.92) was significantly lower than the controls (1.4 ± 1.48) (p=2.94e-6 and p=4.48e-5 respectively). Married BPI patients are more likely to be childless than married controls (marital fertility: BPI: 1.24±1.44, controls: 1.8±1.57; p=0.002). Logistic regression analyses suggested that being a patient with BPI or SZ significantly predicts presence/absence of live offspring after taking into account confounding variables such as age, gender, residence (urban/rural), marital status, consanguinity (BPI: p=0.004, OR=4.67, 95% CI=1.64 - 13.27; SZ: p=0.015, OR=5.41, 95% CI=1.38 - 21.16).

Conclusions: Selected procreational measures among BPI and SZ patients are significantly lower than control individuals. The differences are not attributable to selected demographic variables. Further studies controlling for other confounding variables such as illness severity, medications, birth control use and hormonal levels are warranted.

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439. Serum Levels of Brain-Derived Neurotrophic Factor in Major Depressive Disorder: State and Trait Issues, Clinical Features, and Pharmacological Treatment

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Background: Recent evidence suggests the involvement of Brain-Derived Neurotrophic Factor (BDNF) in depression, but the available evidence is incomplete. We investigated whether abnormalities in serum BDNF levels persist beyond the clinical state of depression and whether serum BDNF levels are related to the clinical features of depression and to the use of antidepressants.

Methods: A cross-sectional design on 382 controls, 962 patients with a current depression, and 700 persons that were in the remission phase of depression.

Results: We found decreased serum levels of BDNF in antidepressant-free currently depressed patients, relative to controls (effect size [Cohen's d] = 0.19), to antidepressant-free persons who were in remission (d = 0.14), and to depressed patients that were treated with an antidepressant (d = 0.23). The effects of antidepressants on serum levels of BDNF effect was confined to the use of selective serotonin reuptake inhibitors (d = 0.24) and St. John's wort (d = 0.51). Serum BDNF levels were found to be unrelated to the clinical features of depression.

Conclusions: Low levels of BDNF appear to be a state abnormality of depression that is present during a depressive episode and normalized during remission. Increases in serum levels of BDNF are specific pharmacological (side) effects of some antidepressants and are not sufficient to directly mediate behavior such as the symptom severity of depression.

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440. Allergen-Specific IgE and Allergy Symptoms are Associated with Depression Scores in Patients with Mood Disorders Exposed to Seasonal pollen Peaks

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Background: Allergic rhinitis and depression are commonly co-occurring and under-diagnosed illnesses. Is this association at a trait (vulnerability) or state (trigger) level, biologically driven or mere psychological? We now examine a hypothesized relationship between allergen specific Immunoglobulin E (IgE), changes in allergy symptoms, and changes in depression scores (typical and atypical) in patients with recurrent mood disorders exposed to natural peaks of tree or ragweed pollen.

Methods: 100 participants from Baltimore or Washington DC (age 43.8 ±10.5, 60 men and 40 women; 53 IgE negative and 47 IgE positive for trees and/or ragweed pollen) with diagnoses of recurrent mood disorder were evaluated blindly, once during a low-pollen period and once during the preceding or subsequent peak high-pollen period. Individuals with any active substance related or psychotic disorders were excluded. Those subjects taking antihistamines and decongestants (unlikely to affect cytokines and inflammatory mediators) were included while subjects taking montelukast or intranasal corticosteroid were excluded. Volumetric sampling for pollen, reported in grains/m3, was conducted as recommended by National Allergy Bureau guidelines. This model allowed matching sensitization to exposure to seasonal allergens. We compared the difference between the Structured Interview Guide for the Hamilton Depression Rating Scale- Seasonal Affective Disorder Version (SIGH-SAD) scores off- and on-allergy seasons. Sensitization was defined at 0.35kUa/L allergen-specific IgE levels using ImmunoCAP 250. Data were analyzed with ANCOVAs with adjustment for CRP level (as a nonspecific inflammation marker).

Results: Typical-depression changes were significantly/ly Related to changes in allergy symptoms (p<0.008), while atypical-depression changes were significantly related to allergen-specific IgE positivity (p<0.045).

Conclusions: To our knowledge, this is the first report of a biological marker of allergic sensitization (allergen-specific IgE) predicting worsening in depressive symptoms during the high pollen season in patients with recurrent mood disorders. Our preliminary findings argue for a “state” level connection between allergy and worsening of mood disorders. Our results also suggest that the link is biologically driven, beyond the mere psychological impact of allergic symptoms, being conducive to research on new preventative and therapeutic targets in the management of mood disorders.

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441. Mood Disorder Susceptibility Gene CACNA1C Modifies Mood-Related Behaviors in Mice and Interacts with Sex to Influence Behavior in Mice and Diagnosis in Humans

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Background: Recent genome-wide association studies have implicated polymorphisms in the gene CACNA1C and a mood disorder diagnosis. CACNA1C codes for CaV1.2, the pore forming subunit of an L-type voltage-gated calcium channel.

Methods: CaCna1c KO mice were bred on a C57BL/6j background. Western
blots and whole-cell voltage-clamp recordings from CA1 pyramidal cells were performed. Behavioral testing in wild type and heterozygous littermates of both genders consisted of holeboard, open field, multiple tests of anxiety-related behaviors, forced swim test, tail suspension test, startle response, amphetamine sensitization, and basic tests of sensorimotor function. Human data from the genome-wide association studies of the NIMH-BP Consortium and the GenRED Consortium was examined utilizing a combined dataset that included 2,021 mood disorder cases (1,223 females and 798 males) and 1,840 controls (837 females and 1,003 males).

Results: We show in mice that Cacna1c haploinsufficiency is associated with decreased CaV1.2 protein levels and decreased dihydropyridine-sensitive calcium currents. Our behavioral results suggest that Cacna1c haploinsufficiency has a protective role in mood disorder-related behaviors, which is more robust in females. We assessed a gene x sex interaction for diagnosis of mood disorders in human male and female subjects. Sex-specific genetic association was seen for two intronic single nucleotide polymorphisms (SNPs) rs2370419 and rs2470411 in CACNA1C, with effects in females (OR=1.6, 1.3), but not in males (OR=0.8, 0.9).

Conclusions: Our preclinical results demonstrate that CACNA1C may play a role in mood disorder pathophysiology, and the combination of human genetic and preclinical data support an interaction between sex, behavior, and diagnosis.

442. Mice Lacking the Oligodendrocyte-Specific Gene Cnp1 Display a Low Emotionality Phenotype in Two Models of Depression.

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Background: 2'-3'- cyclic nucleotide 3'- phosphodiesterase (Cnp1), an oligodendrocyte-specific gene associated with glial-axonal communication, is significantly downregulated in the amygdala of postmortem human major depressive disorder (MDD) subjects, and in the amygdala of mice exposed to the unpredictable chronic mild stress (UCMS) paradigm, suggesting a role for this gene in MDD.

Methods: Baseline emotionality was examined in Cnp1 KO mice at 3, 6, and 9 months, as these mice were reported to have age-associated motor deficits (Cohort 1: N=11-17/group). Two models of depression were also used to assess stress-induced emotionality in Cnp1 KO mice (UCMS - Cohort 2: N=8-12/group; Chronic Corticosterone Administration - Cohort 3: N=10-14/group). Mice were tested in elevated plus maze (EPM), open field (OF), novelty suppressed feeding (NSF), forced swim (FST) and rotarod (RR) tests. Z-scores for emotionality and locomotion were derived across related tests and fecal corticosterone metabolite levels were measured.

Results: Cnp1 KO mice have normal basal emotionality at 3 and 6 months (p>0.05), but lower emotionality at 9 and 12 months (p<0.01). Surprisingly, Cnp1 KO mice exposed to UCMS (p<0.001) or chronic corticosterone treatment (p<0.05) were resistant to developing depression-like symptoms and overall displayed low emotionality and lower levels of corticosterone (p<0.05), all occurring prior to the onset of degenerative motor deficits.

Conclusions: Cnp1 KO mice display a robust low-emotionality phenotype in two models of depression, suggesting that the oligodendrocyte deficits observed in MDD may in fact exert a compensatory effect on the depressive phenotype. Supported by MH083410-02 NIMH

443. Sodium Pump Alpha2 Isoform Hemideficient Mouse as an Animal Model for Mania

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Background: Human bipolar, or manic depressive, illness is characterized by ion dysregulation. Manic subjects have reduced sodium pump (Na,K-ATPase) activity versus euthymia. Na,K-ATPase inhibition in rats utilizing intracerebroventricular administration of ouabain produces a manic-like, lithium-responsive hyperactivity. The findings that the genetic variations in sodium pump alpha2 isoform and a reduction of sodium pump alpha2 expression in post mortem brains of bipolar subjects suggest that deficiency in the alpha2 isoform gene should produce a manic-like, lithium-responsive hyperactivity in animals.

Methods: 129/Black Swiss adult male and female alpha2 KO heterozygotes and wild-type mice were recorded the behavior using an infrared automated activity monitor for 23 hours.

Results: Na,K-ATPase Alpha2 isoform-deficient mice had increased activity at baseline as manifest by greater horizontal activity (22222.17 ± SD18796 vs 17395.88 ± SD37144 number of infrared beam interruptions, P = 0.014), total distance travelled (143064.50 ± SD 24003 vs 101729.63 ± SD 34212cm, P = 0.027), and increase in center time (10066.40 ± SD 579.48 vs 7965.6± SD 552 sec, P = 0.004), and reduced sleep and manifest by reduced rest time over a 23 hour period (71316.67 ± SD 1503.1 vs 74512.0± SD 3265 min, P = 0.047).

Conclusions: Alpha2 KO mouse appears to be a promising genetic animal model for mania. Activity and sleep need to be examined after sleep deprivation, and the effect of lithium need to be examined.

444. Intermediate Phenotypes for Bipolarity Identified in a Genetically Isolated Population

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Background: Investigation of the genetic architecture of intermediate traits associated with bipolar disorder may be a powerful strategy for understanding the genetic basis of this illness.

Methods: Here we sought to characterize the heritability of eleven key quantitative neuropsychological and temperament traits selected for their putative association with bipolar disorder. Study participants to date include 258 members of seven large, multi-generational pedigrees (69 bipolar I probands and 189 of their non-bipolar relatives; 51% female) ascertained from two closely related genetically isolated populations, the Central Valley of Costa Rica and Antioquia, Colombia. Statistical analyses were conducted using SAGE (Statistical Analysis for Genetic Epidemiology), after adjusting for significant covariates.

Results: General cognitive abilities (verbal IQ and memory functions) showed the highest familial aggregation (sibling correlations of 34% and 29%, respectively). Perceptual creativity and delusion—proneness, assessed by www.sobp.org/journal
445. Genome-Wide Association Analysis Implicates a Chromosome 13 QTL, Near the SLITRK Gene Cluster, in Human Cortical Thickness
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Background: Human cortical thickness of various brain regions shows strong association with a number of psychiatric disorders and can therefore be considered an appropriate endophenotype for genetic analysis of psychiatric disorders.

Methods: We have recently performed a genome-wide association analysis using MRI data collected on 486 Mexican Americans across 42 families to identify a QTl strongly implicated in human cortical thickness.

Results: A QTl on chromosome 13 was significantly associated with cortical thickness in the lateral division of the orbitofrontal cortex, with the strongest hit seen for SNP rs2342227 (p = 4.0x10^-10). Associations of this SNP with cortical thickness in a number of other brain regions within the frontal and parietal lobes were also identified (p = 1.5-6.1x10^-5).

Conclusions: The lateral division of the orbitofrontal cortex is thought to be involved primarily in evaluation of punishers and response inhibition as well as in emotion regulation and social development. Further, evidence suggests that it may play a role in bipolar I disorder and obsessive compulsive disorder. The SNP with the strongest association with this region is located within one of the SLITRK gene clusters, which are known to control neurite outgrowth. We are currently re-sequencing the SLITKR1, SLITRKR5, and SLITRKR6 genes to identify novel SNPs and determine likely candidate SNPs that contribute to human cortical thickness, particularly in the lateral division of the orbitofrontal cortex. Identification of the genetic determinates of gray-matter thickness in the normal population will provide empirically derived candidate genes for illnesses associated with gray-matter thinning.

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446. Gene Environment Interactions on Cognitive Reactivity
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Background: A polymorphism in the promoter region of the serotonin transporter gene (SLC6A4) has been shown to influence transcriptional activity and availability of the serotonin transporter (Lesch et al., 1996). The long allele has been associated with more efficient transcription.

Methods: For this study 300 university students were recruited. After DNA collection 5-HTT genotype analyses were conducted. Early childhood maltreatment was measured using the Childhood Trauma Questionnaire (CTQ). Optimism was measured using the learned optimism questionnaire (Seligman M.E.P. 1990). Cognitive Reactivity was measured using the Leiden Index of Depression Sensitivity - Revised (LEIDS-R).

Results: We will present data indicating an interaction of 5-HTTTLPR by environment on cognitive reactivity (CR), a known vulnerability marker of depression. Specifically, they have reported findings of 5-HTTTLPR moderating the influence of childhood emotional abuse on CR.

Conclusions: We will present data indicating an interaction of 5-HTTTLPR by environment on cognitive reactivity in a student sample.
448. A Meta-Analysis of Association of the Serotonin Transporter Gene (5HTTLPR) with Antidepressant Induced Mania

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Background: Antidepressants can trigger a switch to the manic phase of bipolar illness. Identifying genetic risk factors associated with antidepressant induced mania (AIM) may help identify situations when alternative strategies for depression should be considered. This review and meta-analysis was conducted to evaluate the evidence of association between the serotonin transporter gene promoter polymorphism (5HTTLPR) and AIM.

Methods: Medline up to November 2009 was searched for key words bipolar, antidepressant, serotonin transporter, SLC6A4, switch, and mania. Pharmacogenomic studies of AIM that focused on the 5HTTLPR variation in the serotonin transporter gene (SLC6A4) were reviewed.

Results: Five studies (340 AIM+ cases and 543 AIM- controls) were identified that evaluated 5HTTLPR and AIM. A test for heterogeneity indicated significant differences between studies (p=0.006). A trend of association of the S allele with AIM+ status were observed, but a random effects meta-analysis did not detect statistically significant evidence of association (OR=1.40; 95%CI=0.97, 2.02). In an analysis based on subsets of three studies that excluded patients on mood stabilizers, the between-study heterogeneity was less significant (p=0.053), yet the trend of association of the S allele with AIM remained (OR=1.63; 95%CI=1.90, 2.96).

Conclusions: Currently, there is insufficient published data to confirm an association between genetic variation at 5HTTLPR and AIM. Prior studies of this association were highly heterogeneous and had a number of limitations, demonstrating a need for rigorous studies with adequate sample sizes, precisely assessed treatment outcomes and patient characteristics (e.g. rapid cycling, concurrent mood stabilization, and length of antidepressant exposure).

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449. Genome-Wide Combined Linkage/Association Scan Localizes Two QTLs Influencing Human Caudate Volume


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Background: The caudate is associated with higher-order motor control, learning and memory, feedback processing, language and other executive functions. Reduced caudate volume is associated with schizophrenia, bipolar disorder and ADHD. Although caudate volume is under genetic control, the genes influencing this trait are unknown. Here, we conducted genome-wide association analyses to localize the genetic influences on caudate volume.

Methods: 403 Mexican-American individuals from randomly selected extended pedigrees were included in the current analysis. Participants were 62% female and ranged in age from 19 to 85 (mean±SD 47.8±13.5) years. High-resolution T1-weighted images were available for all subjects and caudate volume was calculated with FreeSurfer. Genotyping was conducted with the Illumina HumanHap 550K BeadChip and genetic analyses were performed with SOLAR.

Results: The heritability of caudate volume was 0.685 (p=2.3x10^-10). Two genome-wide significant QTLs were identified with a combined linkage/association analysis: the first near the PRKAR1B gene (nominal p-value = 2.3x10^-8, genome-wide p-value = 0.02) and the second near the LRRTM4 gene (nominal p-value = 1.3x10^-7, genome-wide p-value = 0.049). The PRKAR1B QTL influenced processing speed (p = 0.005), episodic memory (p = 0.04) and working memory (p = 0.05).

Conclusions: Given that the PRKAR1B QTL appears to influence caudate volume and associated cognitive processes, it is a reasonable candidate gene. We are deeply sequencing this gene to identify potential functional variants. Dissection of the genetic basis of normal human brain structural variation should lead to the identification of genes likely to be involved in disorders of brain structure/function.

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450. Polymorphisms in the BDNF Gene are Associated with Antidepressant Treatment Response

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Background: A concatenation of data from animal and human studies suggests the involvement of the neurotrophin system in the central pathology of affective disorders, especially in depression and in antidepressant treatment. Genetic variations within the brain-derived neurotrophic factor (BDNF) gene and its main receptor (NTRK2) may therefore influence the response to antidepressant treatment and might contribute to the development of treatment resistance.

Methods: We performed a pharmacogenetic study in 398 at least moderately depressed Caucasian inpatients participating in the Munich Antidepressant Response Signature (MARS) study. We tested for single marker and haplotype association of 82 SNPs tagging the BDNF and NTRK2 gene regions with antidepressant treatment response. In addition, we performed the combined dexamethasone/CRH (dex/CRH) test in a subgroup of patients at admission (N=242) and prior to discharge from the hospital (N=190).

Results: We identified two SNPs located in the BDNF gene region that were significantly associated with antidepressant treatment response (P=4.9x10^-4 and P=1.5x10^-4) withstanding correction for multiple testing and adjustment for confounding variables. In addition, one SNP showed a gene-dose dependent effect on the improved cortisol response to the dex/CRH test prior to discharge.

Conclusions: These findings provide evidence for an involvement of genetic
variations in the BDNF gene in the antidepressant treatment response and point to a possible role of BDNF in the normalization of an impaired stress hormone regulation.

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451. Fine-Mapping of Genetic Loci Linked to REM-Density in the Munich Vulnerability Study

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Background: The use of endophenotypes in genetic linkage and association studies is supposed to enhance the power for the detection of disease underlying genes. In two previous high-risk family studies of our research group, we could show that rapid eye movement (REM) sleep density constitutes an endophenotype and a genetic vulnerability marker for affective disorders.

Methods: We conducted a SNP-based 100k Illumina whole genome analysis in 82 high-risk family members (11 families, HRFM), 32 of them were unaffected, 33 remitted and 17 suffered from an affective disorder at the time of the investigation and ran a classical parametric linkage (affected/removed vs. never affected HRFM), a variance component and a quantitative trait linkage analysis on sleep REM density.

Results: REM density has a substantial heritability in our cohort (0.79). Linkage analysis resulted in 4 suggestive linkage peaks (LOD score > 2) at loci of the chromosomes 2, 4, 8 and X, that did not hold correction for genome-wide testing. No results were obtained with a classical diagnosis-based linkage approach. Currently, we are fine-mapping these loci. In addition, we are testing whether these linked regions are associated with unipolar depression using the data of our completed genome-wide association studies (about 1500 cases vs. 1500 controls, Illumina 660k).

Conclusions: Our findings suggest the suitability of investigating an endophenotype to pinpoint disease-underlying genes in complex disorders like depression. Genes showing both, linkage with REM density as well as association with unipolar depression would be interesting novel targets for further preclinical and clinical investigations.

452. Comparison of Pharmacogenomic Associations with Clinical Change in Olanzapine/Fluoxetine Combination Treatment of Patients with Treatment Resistant Depression vs. Bipolar I Depression

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Background: Four single nucleotide polymorphisms (SNPs) in 3 genes have been reported to be associated with symptom change during 7-week olanzapine/fluoxetine combination (OFC) treatment in bipolar I depressed (BPD) patients. Genotyping samples from a second study allowed assessment of association of these SNPs with 8-week change in treatment-resistant depression (TRD) during OFC or olanzapine (OLZ) treatment.

Methods: Mixed-effect models for repeated measures, adjusted for baseline Montgomery-Asberg Depression Rating Scale (MADRS), were used to assess association between 8-week change in MADRS and SNPs in genes coding for dopamine-3 receptor D3 (DRD3), histamine H1 receptor (HRH1), and melanocortin 2 receptor (MC2R) in Caucasian patients with TRD treated with OFC (N=63) or OLZ (N=52) after nonresponse following SSRI treatment.

Results: Two-sided p-values for OFC treatment were: HRH1 rs346070, p=0.0356; MC2CR rs4464147, p=0.1884; DRD3 rs6280, p=0.0972; and DRD3 rs16770, p=0.0232. Previously reported greater depressive symptom improvement during OFC treatment of BPD was found for TRD with HRH1 rs346070(C), but not for OLZ, although the direction of the effect was the same (p=0.1228). Improvement was in opposite directions for BPD vs. TRD for DRD3 rs16770.

Conclusions: HRH1 rs346070 may be a relatively non-specific predictor of symptom improvement with pharmacological treatment in both BPD and TRD. Discordant results with the other 3 SNPs may represent either failure to replicate due to lack of statistical power or a fundamental difference in the nature of treatment response in bipolar depression vs. TRD. Supported by Eli Lilly and Company

453. Genome-Wide Association Study of Body Weight in Patients with Major Depression

Stefan Kloiber1, Darina Roeske2, Bertram Müller-Myhsok2, Johannes Hennings1, Florian Holsboer3, Susanne Lucae1

1Pharmacogenetics, Max-Planck-Institute of Psychiatry, Munich, Germany, 2Statistical Genetics, Max-Planck-Institute of Psychiatry, Munich, Germany, 3Director, Max-Planck-Institute of Psychiatry, Munich, Germany

Background: Major depressive disorder and obesity are major public health problems with increasing prevalence during the last decades and epidemiologic and clinical studies suggest a comorbidity between depression and obesity.

Methods: In order to elucidate genetic risk factors underlying this comorbidity we performed a genome wide association study regarding body mass index in our case-control study for major depression (MARS). Genotyping was successfully performed in 415 patients with major depression and 366 psychiatric healthy controls using HumanHap100 and HumanHap300 BeadChip (Illumina Inc., San Diego, California).

Results: We were able to detect a genome-wide significant signal (nominal p-value = 5.89 * 10e-8) on chromosome 6q for body mass index in patients with major depression after quality control and correction for multiple testing. Interaction analysis revealed a significant disease-genotype interaction of depression, body mass index, and genotype. Replication of this result in an independent sample is currently ongoing.

Conclusions: Identifying genetic risk factors for depression and obesity could provide insights in overlapping biological mechanisms of both disorders and, furthermore, could have clinical impact on individualized disease management strategies. Supported by Max Planck Excellence Foundation, German Federal Ministry of Education and Research (BMBF) in the framework of the National Genome Research Network (NGFN) Foerderkennzeichen 01GS0481
454. Genome-Wide Gene-Expression Profiles Following Glucocorticoid Stimulation Associated with Major Depression

Andreas Menke, Benno Puetz, Peter Weber, Andreas Eichelkraut, Monika Rex-Haffner, Torsten Klengel, Maryia Gonik, Manfred Uhr, Jan Deussing, Florian Holsboer, Bertram Mueller Myhso, Elisabeth B. Binder

RG Molecular Genetics of Depression, Max Planck Institute of Psychiatry, Munich, Germany

Background: Investigation of peripheral blood derived RNA may reveal biomarkers for affective disorders. Because of previous inconsistent results from baseline gene-expression profiling we applied a dexamethasone (dex) challenge test to compare glucocorticoid receptor (GR) activation mediated changes in gene-expression between depressed patients and healthy controls.

Methods: For GR activation, whole blood was collected at 6 pm before and three hours after ingestion of 1.5mg of dex. The next day we performed the combined dex/corticortinophor releasing hormone (dex/CRH) test. RNA was collected in two independent samples of 18 in-patients with major depression and 18 controls (discovery sample) and 11 vs. 13 in the replication sample. RNA was hybridized to Illumina HumanHT-expression-BeadChips.

Results: Dex led to a significant suppression of cortisol and ACTH after 3h. In controls, 786 transcripts were regulated by dex in both samples with nominal p<0.05 and 272 transcripts in patients. When comparing genes with significant difference in the baseline samples between cases and controls in both discovery (226 transcripts at p<0.01) and replication samples (817 transcripts), no genes overlapped. In contrast, 450 and 393 transcripts were differentially regulated between cases and controls in the post-dex condition with 33 overlapping transcripts. Comparing the delta gene-expression between cases and controls revealed 45 regulated transcripts in both samples with p<0.05, among them FKBP5, which could be validated with RT-PCR.

Conclusions: The results may indicate that the use of stimulated gene expression pattern in whole blood may yield more consistent differences between patients and controls in major depression than baseline expression pattern. Supported by FKZ 01GS0481

455. Depressive Response to Tryptophan Depletion: Lack of Genetic Association with Serotonin Related Candidate Genes

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Background: Acute Tryptophan (TRP) Depletion [ATD] has been proposed as a phenotype for major affective disorders based on their ability to induce brief and reversible depressive responses in subjects considered at risk for depression.

Methods: We conducted ATD in 60 subjects with personal and family history of major depression but who were in remission and medication-free for at least three months. ATD involved active depletion and sham condition in a double blind, controlled, crossover design. ATD was accomplished by ingestion of a TRP-free 15 amino acid drink or a TRP-supplemented 16 amino acid drink for control condition. Genotyping of several candidate gene polymorphisms relevant to monoamine synthesis, transport, receptor activity, degradation and intracellular signaling was conducted. ANOVA with repeated measures was used to assess time, test condition, and interaction with specific genes.

Results: There was a main effect of TIME F=2.39, df=3, p=0.08; TEST F=2.53, df=1, p=0.11; and TIME * TEST interaction F=7.5, df=3, p=0.02. There were no significant interactions of TIME or TEST by GENE for the following candidate genes: SERT (l/s, including triallelic G-A, and S13), HTR1A, HTR2A, TPH2, MAOA, MAOB, BDNF, AP-2Beta, DRD2, DRD3, DRD4, DBH, DAT1, and COMT.

Conclusions: This is the largest study of this kind conducted to date. The level of depressive response during testing was modest, and no evidence of interaction was found with any of the primary or secondary genes of interest. These data bring into question the utility of mood response during TRP depletion as an alternative phenotype to study depression. Supported by R01 MH066235

456. The Effect of Life Stress on Reward-Related Brain Function is Moderated by 5-HTTLPR Genotype

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Background: The short (S) allele of the serotonin transporter promoter linked polymorphic region (5-HTTLPR) has been associated with increased risk of depression following stressful life events. Since prior research has suggested that stress-induced anhedonia may be responsible for some of the depressogenic effects of stress, and a more responsive neural reward circuitry may be implicated in resilience to trauma, we hypothesized that stress-induced changes in reward-related ventral striatum (VS) function may partly explain differential susceptibility to depression observed as a function of 5-HTTLPR genotype.

Methods: Archival genetic, neuroimaging, and self-report data were available for 69 Caucasian participants. Using the median-split of the number of self-reported stressful life events, we examined the independent and interactive effects of stress and 5-HTTLPR genotype on VS reactivity in response to monetary reward.

Results: When controlling for gender, there was a significant genotype-by-stress interaction on VS reactivity (F(1,64)=4.37, p<0.04) such that L homozygotes in the high stress group (n=11) had significantly higher right VS reactivity than those in the low stress group (n=11, F(1,19)=5.66, p<0.03), while stress had no effect on VS reactivity in S carriers (high stress group, n=20; low stress group, n=27; p=0.65).

Conclusions: Our results indicate that the effect of stressful life events on reward-related VS function is moderated by the 5-HTTLPR. The stress-related increase in VS reactivity to reward in L homozygotes may reflect a mechanism conferring relative resiliency to depression in the wake of life adversity absent in S carriers.
**457. Association between DNA Methylation and Maternal Assessment of Early Childhood Behavior in High-Risk Infants**

**James Schroeder**

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**Background:** Psychiatric disorders during pregnancy may lead to adverse behavioral development in offspring. We hypothesize that perinatal maternal mental illness influences offspring neurobehavioral development and that epigenetic mechanisms including DNA methylation partially mediate such influences.

**Methods:** This study evaluated the offspring of women with psychiatric disorders who were followed prospectively throughout pregnancy. We evaluated the association between methylation patterns in umbilical cord blood DNA using the Illumina HumanMethylation27 BeadChip and t-scores of the DSM-oriented CBCL scales in 20 children from 1.5-4.5 years. We analyzed each of the 27,578 CpG sites with linear regression accounting for chip effects using a random effects model, adjusting for maternal depression (BDI) at the time of CBCL completion.

**Results:** Many CpG loci were nominally associated with attention deficit (ADD; 3334), affective (AFF; 1262), anxiety (ANX; 1681), oppositional defiant (ODD; 1044) and pervasive development (PDD; 1834) problems. Table 1 shows the CpG locus associated with the lowest observed p-value for each scale. Although none of these results met criteria for experiment-wide significance after Bonferroni correction, $p<0.05$, they were large effects given our limited sample size.

**Conclusions:** Our results provide preliminary evidence in support of our hypothesis that epigenetic alterations may be associated with behavioral outcomes in high-risk children. A larger, ongoing study is underway to validate these findings.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Target ID</th>
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<th>P</th>
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<td>NUP98</td>
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Supported by NIH grants P50 MH077928 (ZNS) and RC1MH088609 (AKS/PAB)

**458. Relationship Between FKBP5 Polymorphisms and Depression Symptoms Among Kidney Transplant Recipients**

**Gen Shinozaki**1,2, Sheila Jowsey1, Hatem Amer3, Joanna M. Biernacka1,4, Alexis Sharp1, Peter Meng1, Karen Chia1, David Mrazek1, Mark A. Frye1

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**Background:** It has been demonstrated that several polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Also, subjects with the same polymorphisms in FKBP5 and a history of child abuse have been reported to be at an increased risk for post traumatic stress disorder (PTSD). However, there is no replication showing the polymorphisms as vulnerability factors for PTSD.

**Methods:** A retrospective analysis was conducted of the electronic medical records of 135 adult kidney transplant recipients at Mayo Clinic Rochester MN from 2001-2006. Depression severity after kidney transplant surgery was measured by PHQ9, and stored blood was genotyped for Serotonin-Transporter (SLC6A4), Brain-Derived-Neurotrophic-Factor (BDNF), Cathecholamine-O-Methyltransferase (COMT), Corticotrophin-Releasing Hormone-Receptor (CRHR1) and FKBP5. In total 13 polymorphisms were genotyped. Spearman correlations were utilized for statistical analysis.

**Results:** Polymorphisms in genes other than FKBP5 were not associated with PHQ9 scores. However, the rare alleles at three out of four SNPs in FKBP5 (rs360780, rs2996158 and rs9470080) were associated with increased PHQ9 scores ($p<0.05$), while the last FKBP5 SNP (rs3800373) showed a trend of association ($p=0.10$). All four SNPs are in strong linkage disequilibrium. The direction of the associations was consistent with the previous reports.

**Conclusions:** Polymorphisms in FKBP5 are associated with higher depression score in kidney transplant recipients. These genotypes can be one of many genetic factors associated with the individual difference for stress vulnerability and resiliency for mental illnesses such as depression and PTSD.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype (N)</th>
<th>Glu/Cr</th>
<th>Glu/T1</th>
<th>Glu/T2</th>
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<td>rs12249040</td>
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<td>0.905</td>
<td>155.90 (26.96)</td>
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<td>27.91 (14.67)</td>
<td>113.15 (16.57)</td>
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<td>AA/AG (14)</td>
<td>1.38 (0.14)</td>
<td>144.44 (22.20)</td>
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</tbody>
</table>

Supported by NARSAD
460. Childhood Abuse and Increased Risk for Anger in Depression during Adulthood: The Moderating Role of MAOA Genotype and Gender


Clinical Psychology, Leiden University, Leiden, Netherlands

Background: A functional polymorphism in the monoamine oxidase A (MAOA) gene results in variants with high or low MAOA mRNA expression and enzyme activity. Previous research has shown that this polymorphism moderates the association between childhood abuse and aggressive or antisocial behaviour in later life. Moreover, adolescents with low MAOA activity score higher on depressive symptomatology than those with high MAOA activity. In men, the relationship of MAOA genotype and aggression was restricted to individuals with a history of childhood abuse. Childhood abuse also leads to elevated rates of depression in adolescence and later life. The purpose of the current study is to investigate the relationship between MAOA genotype, childhood abuse history and a subtype of depression that is characterized by anger/aggression.

Methods: We measured depression, cognitive vulnerability to depression and (trait and state) anger in 300 North-European college students. MAOA genotype was also determined. Gender and history of childhood abuse were included as potential moderators of this relationship.

Results: Men with low MAOA activity scored significantly higher on trait anger and aggression reactivity than men with high MAOA activity. These effects were not observed in women. Moreover, the effects were more pronounced in men with a history of childhood abuse.

Conclusions: Men with low MAOA activity have higher trait anger scores and also have more aggressive thoughts during dysphoric mood states. These effects were more pronounced in men with a history of childhood abuse.

461. Dopamine Receptor D2 (DRD2) Polymorphism and Psychological Resilience in a Highly Traumatized Urban Population

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Background: Biological mechanisms underpinning psychological resilience are largely unknown. Given that DRD2 polymorphisms have been associated with suicide, substance dependence, and depression, we investigated associations between DRD2 polymorphisms and resilience in individuals with a history of trauma.

Methods: In this cross-sectional study of 805 participants, we assessed for history of childhood abuse, other trauma exposure, and current depressive symptoms (with the Beck Depression Inventory (BDI)), and PTSD symptoms for history of childhood abuse, other trauma exposure, current depressive (BDI <=10) or PTSD symptoms (DSM-IV PTSD criteria and current moderate/severe depressive symptoms (BDI >=19) or moderate/severe PTSD symptoms (DSM-IV PTSD criteria met and mPSS >=26). Salivary DNA was collected and 19 SNPs spanning the DRD2 gene were analyzed. In addition, we measured attentional bias with diverse dot probe in a subset of participants.

Results: After Bonferroni correction for multiple testing, DRD2 rs1799978 was significantly associated with resilience (uncorrected p=0.0016; corrected p=0.030). After adjusting for severity of childhood abuse and other trauma exposure and sex using multiple logistic regression, AA genotype was more associated with resilience than GA/GG genotype (OR=2.0, p=0.004). Consistently, AA individuals showed a slight attentional bias away from threatening faces (mean bias score = -7.3; SD=44.2) while GA/GG individuals showed an attentional bias toward threatening faces (mean bias score=33.3; SD=61.1).

Conclusions: DRD2rs1799978 is a promising genetic marker for resilience; our results await validation. Supported by APIRE fellowship award, NIH grant UL RR025008, MH071537, M01RR00039, American Foundation for suicide prevention, Burroughs Wellcome Fund

462. Cholesterol and CSF 5-HIAA in Attempted Suicide

Peter Asellus, Peter Nordstrom, Jussi Jokinen

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Background: Low serum cholesterol has been linked to suicide and violent behaviour. The same kind of associations has been reported regarding low levels of 5-hydroxyindolacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) and suicidal behaviour. The hypothesis of the link between serum cholesterol and suicide incorporate serotonin. It proposes that low cholesterol is related to reduced serotonergic neurotransmission, which in turn, is linked to violent and suicidal behaviour. A correlation between CSF 5-HIAA and serum cholesterol has been shown in animal-studies, but has not been found in humans. The aim was to study the interrelationship between serum cholesterol and CSF 5-HIAA in suicide attempters. Since both cholesterol and CSF 5-HIAA are associated with suicide and violent suicide-attempts, we also investigated the correlation with suicide, violent suicide attempt method, suicide intent, hopelessness and depression severity.

Methods: Serum total cholesterol and CSF 5-HIAA was measured in 42 medication free suicide attempters. Patients were assessed with Beck’s Hopelessness scale (BHS), Suicide Intent Scale (SIS) and Montgomery-Åsberg depression rating scale (MADRS) and followed-up for causes of death.

Results: Serum total cholesterol and CSF 5-HIAA showed a significant positive correlation adjusted for age, body mass index and substance abuse diagnosis. Cholesterol and CSF 5-HIAA levels did not differ between violent and non-violent suicide attempters or between suicide completers and survivors.

Conclusions: These findings indicate that the serotonergic system may be connected to serum cholesterol in patients with a recent suicide attempt.

463. Serotonin Transporter (SERT) Polymorphisms and Corticotropin-Releasing Factor (CRF) Levels in Alcoholism and Suicide

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1Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX, 2Psychiatry, Medical Colleges of Georgia, Augusta, GA

Background: Hypothalamic-pituitary axis, serotonergic, and stress pathways are involved in the pathogenesis of mood disorders, suicide and alcoholism, and potentially mediated by corticotropin-releasing factor(CRF), CRF receptors(R1,R2) and serotonin transporter(SERT). This study examines SERT polymorphisms and CRF receptor mRNA levels in alcoholism and suicide.

Methods: Postmortem brain tissue from suicidal alcoholics(n=5), non-suicidal alcoholics(n=4) and normal controls(n=4) was obtained from the Southwest Brain Bank. Diagnoses are made by consensus diagnosis of next-of-kin interviews and medical records. RNA from PFC(BA9), AC(BA24) and...
644. Serotonin Receptor Levels and Mood States in Alcoholism and Suicide

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¹Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX, ²Psychiatry, Medical Colleges of Georgia, Augusta, GA

Background: The prefrontal (PFC) and anterior cingulate (AC) cortices are components of the limbic system that mediate cognitive, emotional and autonomic processes. Serotonergic (5HT) disruptions in these connections are implicated in psychiatric disorders. Impulsivity in relation to suicide and alcoholism has been associated with markers of reduced 5HT function. Our objective is to elucidate the relationship between 5HT receptor expression and mood state in these groups.

Methods: Postmortem brain tissue from alcoholics who committed suicide (n=5), alcoholics who did not die from suicide (n=4) and normal controls (n=4) was obtained from the Southwest Brain Bank. Diagnoses are made by consensus diagnosis of next-of-kin interviews and medical records. RNA isolated from PFC(BA9), AC(BA24) and visual cortex (BA18) was used for qRT-PCR of SERT, 5HT1a and 5HT2a mRNA. Data was analyzed using Pearson correlations with significance at p≤0.05.

Results: Suicidal alcoholics showed down-regulation of SERT and up-regulation of 5HT2a in BA24 (0.905; p<.05). MADRS scores of suicidal alcoholics are directly correlated with SERT in BA9 (0.964; p<.01) and BA24 (0.904; p<.05) and inversely correlated with 5HT2a in BA18 (0.928; p<.05). Impulsivity is correlated with BA9 SERT (0.937; p<.05) and inversely correlated with BA18 5HT2a (0.926; p<.05). In non-suicidal alcoholics, 5-HT2a is inversely correlated with 5HT1a (0.971; p<.05) in BA24. MADRS scores in these subjects are inversely correlated with BA18 5HT2a (0.976; p<.05). Impulsivity scores are correlated with 5HT1a (0.986; p<.05) and inversely correlated with 5HT2a in BA24 (0.995; p<.01).

Conclusions: Findings emphasize the relationship of decreased 5HT functioning in suicidal and non-suicidal alcoholics in BA24. They also demonstrate altered relationships between the receptors/SERT and impulsivity, aggression, and depression across diagnoses.

Supported by Peter F. McManus Charitable Trust

645. Serum Levels of IL6, IL10 and TNF-Alpha in Patients with Bipolar Disorder in Euthymia and with Schizophrenia: Differences in Pro and Anti-Inflammatory Balance

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Background: Involvement of inflammatory processes in the pathophysiology of psychiatric disorders has been suggested. Cytokines have received special attention as potential mediators of the interaction between immune and neuroendocrine systems. Previous reports have suggested a proinflammatory state associated with both Bipolar Disorder (BD) and Schizophrenia (SZ). However, they did not compare cytokine levels between the two disorders.

Methods: We recruited 20 subjects with BD during euthymia, 55 chronic stabilized schizophrenics and 80 healthy volunteers. Cytokines TNF-α, IL-6, and IL-10 were examined by flow cytometry.

Results: IL-6 was significantly increased in patients with SZ when compared to either controls (p<0.0001) or euthymic patients with BD (p<0.0001). IL-6 levels were not different in controls compared to euthymic BD patients (p=0.357). IL-10 was significantly lower in controls compared to SZ (p<0.001) or BD (p=0.004). There was no significant difference in TNF-α serum levels among the three groups (p=0.284). The significance did not change when patients were separated by gender and there was no correlation with antipsychotic dose and cytokine levels in patients with SZ.

Conclusions: These findings suggest that SZ is associated with a proinflammatory state, while BD out of a mood episode not. Interestingly, anti-inflammatory factor IL-10 was increased either in BD or SZ, which may suggest a different pattern of inflammatory balance between these two disorders. Besides the role of cytokines as possible biomarkers for disease activity or treatment response; this study provides further support to investigate the immune system as a target for future treatment development.

Supported by CNPq

646. MR-Spectroscopy of the Dorsolateral Prefrontal Cortex and Anterior Cingulum of Patients with Major Depression: Comparism with Healthy Controls and Follow-Up after a 4-Week Naturalistic Treatment Period

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Background: Regional cerebral abnormalities, most consistently involving the left dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) have been repeatedly reported in depressed patients compared to healthy controls. Furthermore, amelioration of symptoms was frequently reported to be correlated with activity-changes in both structures.

Methods: 3 Tesla proton magnetic resonance spectroscopic examinations of...
the left DLPFC and ACC were conducted in 33 patients with unipolar major depression and 28 age- and gender matched healthy controls. Concentrations of N-acetyl-aspartate (NAA), creatine (Cr), choline compounds (Cho) and glutamate (Glu) were measured in patients and compared to healthy controls. After 4 weeks of antidepressant treatment, patients underwent a second follow-up scan.

Results: No significant changes could be detected for NAA, pCr, Cho and Glu between Patients and controls. However, a significant negative correlation (p<0.05) between age and NAA-levels was found.

Patients after 4 weeks of treatment showed a significant correlation between reduction in Hamilton Depression Scale and increase of NAA-levels in the DLPFC (p<0.05).

Conclusions: Consistent with the literature, a significant correlation was observed between age and NAA-levels of the DLPFC and ACC in all subjects. Clinical improvement of depressed patients was accompanied by a relative increase of NAA levels in both frontal lobe structures, although significant only in the DLPFC. These preliminary findings provide new evidence of functional neurochemical marker alterations under antidepressant treatment. In addition, these results emphasize the functional relevance of the NAA-signal in MRS as a potential marker for treatment-related neurotrophic effects.

467. Increased Uric Acid Levels in Drug-Naïve Subjects with Bipolar Disorder during First Manic Episode

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Background: Recent evidence suggests that dysfunctions of the purinergic system may play a role in the pathophysiology and therapeutics of bipolar disorder (BPD). Uric acid represents a key downstream protein in this system, and besides being a potential marker of treatment response, high plasma levels may represent a state marker during mania. However, it is unknown whether increased uric acid levels are also present during the early phases of BPD in never medicated subjects.

Methods: Twenty drug-naive BPD subjects during the first manic episode, along with 24 matched healthy control subjects (HC) were enrolled in this study. Plasma levels of uric acid and oxidative stress markers (superoxide dismutase, catalase and TBARS) were measured. We hypothesized that acutely manic patients would have higher plasma uric acid levels compared to healthy controls.

Results: We found that acutely manic patients had significantly higher plasma uric acid levels (4.85 ± 1.60 mg/dL) compared to healthy controls (2.96 ± 0.63 mg/dL; p < 0.001; F = 28.1). Bipolar patients also showed an increase in oxidative stress parameters. Finally, plasma uric acid levels showed a significant correlation with oxidative stress parameters levels in the total sample.

Conclusions: The present results support the role for purinergic system dysfunction in bipolar disorder even early on in the illness. Dysfunction of the purinergic and oxidative stress parameters were not do to the chronic effects of illness or medication exposure. Our findings in first episode mania suggest a novel pathophysiological mechanism in bipolar disorder.

Supported by CNPq

468. CSF 5-HIAA, Childhood Trauma and Violent Behaviour in Suicide Attempters

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Background: Serotonin is implicated in impaired impulse control, aggression and suicidal behavior. Low cerebrospinal fluid (CSF) concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) are associated with suicide risk. CSF 5-HIAA concentrations have both genetic and environmental determinants. Childhood trauma may have an effect on central monoamine function as an adult. The aim of this study was to assess the relationship of CSF 5-HIAA and the exposure to and the expression of violence in childhood and during adult life measured with the Karolinska Interpersonal Violence (KIV) rating scales.

Methods: 41 medication free suicide attempters underwent lumbar puncture and were assessed with the Karolinska Interpersonal Violence (KIV) rating scales to assess both the exposure to and the expression of violence in childhood and during adult life.

Results: In women, but not in men, CSF 5-HIAA showed a significant negative correlation to exposure to violence during the childhood. In the non-traumatized group, the CSF 5-HIAA showed a significant negative correlation to expressed violent behaviour in childhood.

Conclusions: Although central serotonergic function has important genetic determinants, exposure to childhood trauma may also affect serotonergic function. Supported by Unfunde

469. Antidepressant Use in Hypertensive Patients: A Primary Care Study

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Background: The RAAS is partially responsible for regulating the HPA axis. Small open label reports endorsed the antidepressant properties of some ACE inhibitors and ARBII’s. Statins inhibit the enzyme responsible for a cascade of hormones some of which may have an impact on the etiology of depression. This is the first report of the impact of medications used to treat hypertension and hyperlipidemia on antidepressant use in a primary care setting.

Methods: A retrospective chart review was performed on all the patients currently being seen in the office of an internist. Demographic information and medication history were collected for all patients with a diagnosis of hypertension and who had been seen at least twice and for a period of over 3 months.

Results: 378 patients were diagnosed with hypertension. Their average age was 63 (±14, range 28-96). 208 patients were female, 170 were male. 24% of patients were also taking an antidepressant. 229 patients were taking one medication for hypertension. 19% of patients taking an ACE inhibitor were on an antidepressant, 25% of patients on an ARB, and 38% of patients on a beta blocker. Among 202 statin users, patients taking simvastatin had the least frequent use of antidepressants (16%) followed by atorvastatin(23%), pravastatin and lovastatin (25%) and rosuvastatin(36%). 10% of patients on a combination of a statin and an ARBII were on an antidepressant compared to 17% of those on a combination of an ACE inhibitor and a statin.

Conclusions: Primary care physicians prescribe antidepressants more often than psychiatrists. Hypertension and hyperlipidemia are 2 other frequently treated conditions in this setting. The selective use of some statins with RAAS affecting medications may reduce the need for antidepressant medications, especially simvastatin in combination with an ARBII.
470. The MAO A Transcriptional Repressor, R1, is Decreased in Human Major Depressive Disorder (MDD) and in Chronic Social Stress in Rodents

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Background: Chronic stress, associated with secretion of glucocorticoids, is a risk factor for depression. Glucocorticoids reportedly induce apoptosis and increase the activity of monoamine oxidase (MAO), an enzyme for the degradation of monoamine neurotransmitters. R1 has recently been identified as a transcriptional repressor for MAO A and is involved in MAO A-mediated neuronal apoptosis. Altered expression of R1 may be an important factor in the pathophysiology of MDD as well as rats exposed to chronic social stress.

Methods: The expression of R1 was examined by Western Blot using postmortem prefrontal cortex from (1) ten pairs of human subjects with MDD and normal control subjects, and (2) ten adult male Wistar rats exposed to chronic social defeat stress compared to controls. The “resident-intruder” stress paradigm was used for four weeks.

Results: The expression of R1 protein was significantly decreased by ~42 percent (P < 0.01) in the human subjects with MDD as compared to normal controls. Similarly the expression of R1 was significantly decreased by ~29 percent (P < 0.05) in the rats treated with stress.

Conclusions: The level of R1 protein was significantly reduced in subjects with MDD and in chronically stressed rats, as compared to appropriate controls. Interestingly, Meyer et al. (2006) observed widespread increases in MAO A levels in the brains of living subjects with MDD. Therefore, the decreased expression of this transcription factor in depression or stressful conditions may enhance the expression of MAO A, lower monoamine neurotransmitter levels and contribute to the psychopathology of depressive disorders.

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471. Metallothionein Gene Expression and Genetic Variants: Implications for Mood Disorders and Suicide

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Background: Mood disorders patients are at high risk for suicide, however, only a subset of mood disorder patients attempt or complete suicide. The purpose of this study was to investigate brain gene expression changes associated with suicide in mood disorder patients in the anterior cingulate cortex (ACC) and the nucleus accumbens (NACC).

Methods: Brain gene expression levels were investigated (HG-U133 Plus2.0) in a total sample of 28 suicides and 16 non suicides mood disorder subjects. Statistical analysis was performed using Partek and an ANCOVA model used to identify significant genes while controlling for confounding factors. Confirmation of these results was performed by qPCR. Promoter regions of genes of interest were scanned for SNPs by High Resolution Melting (HRM) and genotypes regressed against expression levels to find regulatory variants.

Results: A total of 136 significant genes were observed in the ACC and 146 in the NACC. Several metallothionein 1 and 2 subfamily genes, located in 16q13 whose expression is controlled by glucocorticoids, were down-regulated in suicides in the NACC and ACC. Ingenuity Pathway Analysis of significant genes confirmed the involvement of glucocorticoid receptor signaling in suicide. Confirmation of the reduction of metallothionein genes was performed for selected genes by qPCR. Variants in the promoter of some of these genes possibly affecting expression were observed by HRM and confirmed by sequencing.

Conclusions: The present study reveals a link between metallothioneins reduction and suicide, suggesting that an altered response to cortisol may be involved in suicide susceptibility in mood disorder patients.

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472. Lack of Effect of Ketamine on Cortical Glutamate and Glutamine in Healthy Volunteers: A Proton Magnetic Resonance Spectroscopy Study

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Background: Ketamine is an NMDA antagonist that in preclinical studies increases glutamate outflow in the prefrontal cortex. Using proton Magnetic Resonance Spectroscopy (MRS), loading doses of ketamine have been associated with transient increases in glutamine in the anterior cingulate cortex (ACC) of healthy volunteers. Major depression is associated with decreased levels of glutamate and glutamine (Glx) in the ACC that normalise with clinical recovery. The gradual infusion of low dose ketamine has also been associated with temporary clinical improvement in patients with treatment resistant depression. The present study aimed to test whether a similar low dose ketamine infusion would increase cortical Glx levels in healthy volunteers.

Methods: Healthy volunteers received an intravenous infusion of ketamine (0.5 mg kg⁻¹, n=8) or saline (n=7) over 40 minutes. MRS measurements were obtained at baseline, during, and at the end of the infusion. PRESS and PRESS-J measurements were taken from a 30x20x20mm voxel placed in the ACC. Mental state effects were assessed by the Clinician Administered Dissociative States Scale (CADSS) and Brief Psychiatric Rating Scale (BPRS).

Results: The 40 minute continuous infusion of ketamine had significant effects on mental state with increased scores on both CADSS (ketamine 23.1±3.0; saline 0.6±0.4; p<0.001) and BPRS (ketamine 9.5±2.2; saline 0.29±0.29; p=0.005). There was no effect of ketamine on the levels of Glx (F(3,39)=1.401, p=0.26) or glutamate (F(2,6,34.6)=0.039, p=0.98).

Conclusions: This study suggests that the gradual infusion of low dose ketamine does not cause proton MRS visible changes in cortical glutamate or glutamine in healthy volunteers.

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473. Gender-Specific Gene Expression of a Novel Zinc Finger Transcription Factor, KLF7, in the Prefrontal Cortex of Subjects with Major Depression

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Background: Background: Considerable evidence from various investigations has implicated brain-derived neurotrophic factor (BDNF) in the pathophysiology of major depressive disorder (MDD). KLF7, of the mammalian family of C2H2 zinc finger Krüppel-like transcription factors (KLFs) has been proposed to play a role in neurogenesis due to its early expression in postmitotic neurons during differentiation of the cerebral cortex. Given the putative roles of KLF7 in neurogenesis and TrkB receptor regulation, it is possible that KLF7 may play an important role in the pathophysiology of MDD.

Methods: Preliminary DNA microarray experiments identified gender-specific prefrontal cortical (PFC) gene expression profiles of MDD subjects. Specific gene transcripts were selected and subjected to real-time PCR measurement for confirmation and further quantification in PFC samples from 13 female and 12 male MDD subjects and equal numbers of gender-matched control subjects.

Results: KLF7 mRNA levels were significantly (over 30%) decreased in the PFC of female MDD subjects as compared to gender-matched controls. In contrast, KLF7 mRNA levels were significantly (over 30%) increased in the PFC samples of male MDD subjects relative to gender-matched control subjects.

Conclusions: Our study discovered a novel gene, KLF7, shows gender-specific changes in PFC mRNA concentrations of subjects with MDD. Currently, little is known about the function of KLF7 in the adult prefrontal cortex or the mechanisms that regulate its expression. However, the potential link to BDNF signaling and TrkB receptor regulation provides an interesting avenue to further investigate KLF7 and its potential role in the biological mechanisms underlying gender differences in major depression. Supported by Public Health Service Grants P20 RR17701

474. Magnetic Resonance Spectroscopy Imaging of Differences Between Unmedicated Bipolar and Unipolar Depression

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Background: This study investigated whether Bipolar Depression (BDD) and Unipolar Major Depressive Disorder (MDD) could be differentiated using magnetic resonance spectroscopy imaging (MRSI).

Methods: Unmedicated BDD patients (n = 9, 40+9 yrs, 6M) and unmedicated MDD (n=17, 36+9 yrs, 7 M), were included. MRSI data were acquired on a 3T Tim-Trio (Siemens Healthcare) MRI scanner using a 12-channel head coil array, a nominal voxel size of 2.8 ml (13.75 x 13.75 x 15 mm³), TR = 1500 ms and TE = 30 ms, in a 15 mm thick axial slice that was placed along the AC-PC line. The slice covered the following regions of interest (ROIs): pregenual anterior cingulate cortex (ACC) and thalamus. Single voxel spectra from each ROI were quantified using LCModel and metabolite concentrations are given as ratios to total creatine (tCr) (Cramer-Rao lower bound fit ≤ 15%). The resulting metabolite ratios for N-Acetylaspartate (NAA), choline (Cho), myo-inositol (mI), glutamate (Glu), glutamate + glutamine (Glx), and lactate (Lac) were compared between the groups using a student’s t-test for each ROI.

Results: The following trend level differences were seen between BDD and MDD: Right Thalamus: Glu/Cre (MDD (n = 12) < BDD (n = 8), p = 0.1), NAA/Cr (BDD (n = 8) < MDD (n = 15), p = 0.09); Left ACC: Lactate/Cr (BDD (n = 6) > MDD (n = 12), p = 0.06).

Conclusions: Preliminary results from this study suggest that MRS may be used to identify differences between BDD and MDD patients. Supported by NIMH

475. Dysregulated Activation of Prefrontal and Limbic Regions in Emotional Processing in Bipolar Disorder: A Meta-Analysis

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Background: Bipolar disorder patients frequently exhibit abnormalities in processing emotional stimuli at both the behavioral and neurophysiological level. However, findings across studies has been inconsistent. The current study uses quantitative meta-analysis to synthesize the functional neuroimaging results from studies of emotional processing in bipolar disorder.

Methods: Eleven English-language, peer-reviewed articles published prior to October 2009 were identified using the PubMed database. All studies provided whole-brain analyses of functional magnetic resonance imaging (fMRI) of positive or negative emotional processing by adult patients with bipolar disorder. Activation Likelihood Estimation (ALE) modeling reported activation maxima as the center of a three-dimensional Gaussian function, with statistical thresholding and correction for multiple comparisons.

Results: Relative to healthy subjects, bipolar patients showed greater activation in the amygdala and parahippocampal region, and less activation in the superior frontal gyrus and anterior cingulate during both positive and negative emotional processing. (See Figure where red/yellow represents increased activation and blue/green represents decreased activation.) These findings were present across mood states of the bipolar patient sample.

Conclusions: This meta-analysis provides a unifying summary of altered neural activation exhibited by bipolar disorder patients while processing emotional stimuli. The meta-analytic findings demonstrate relative hyper-activation in the medial temporal and limbic areas, and relative hypo-activation in the frontal cortex. Our results highlight the role of corticolimbic network dysregulation in affective processing in bipolar disorder.
476. Mood State Cannot be Ignored in Morphometric Studies of Bipolar Disorder: A Longitudinal Within-Subjects Study of Brain Structure

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**Background:** MRI studies of patients with bipolar disorder have aggregated patients in different mood states when comparing them to healthy control subjects. However, several recent studies using between-subjects comparisons suggest neural plasticity is associated with mood state.

**Methods:** Seven patients (average age = 42 years) with bipolar I disorder received 1.5T MRI scans during periods of depression and euthymia. Patients were taking various psychotropic medications. Voxel-based morphometry (VBM) was performed using SPM8 with a height threshold of p < .005 (uncorrected).

**Results:** Results are illustrated in the Figure (increased density in red/yellow; decreased density in blue/green). Compared to euthymia, patients scanned during depressed phases showed significant decreases in gray matter density of the superior (BA 10) and inferior (BA 46) frontal gyri as well as the anterior cingulate (BA 32). Conversely, during depressive episodes gray matter density increases were observed in fusiform and inferior temporal gyri (BA 20), in subgenual prefrontal cortex (BA 25), and in the parahippocampal gyrus.

**Conclusions:** The magnitude of the within-subject effects suggests a striking degree of neural plasticity associated with mood state. These findings may explain some of the variability of prior neuroimaging studies of bipolar disorder, and suggest future studies should take mood state into account.

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477. Positron Emission Tomography and Functional MRI to Assess Mechanism of Action of Aripiprazole as an Antidepressant Augmentation Agent

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**Background:** Aripiprazole (ARP) is an atypical antipsychotic agent and partial dopamine 2 (D2) agonist recently FDA-approved as an augmentation agent in major depressive disorder (MDD) unresponsive to antidepressant monotherapy. Several large, double-blinded studies have replicated ARP’s effectiveness in augmenting unresponsive MDD; however, little is known about how ARP provides this antidepressant response. We hypothesize ARP’s antidepressant mechanism of action to be based on the dopaminergic system and test this using functional neuroimaging.

**Methods:** Seven subjects with MDD (minimum Hamilton Depression Scale = 18; recruitment goal N = 45) receive 6 weeks of SSRI (Lexapro 10-20mg) with adjunctive placebo. Subjects responding to treatment (> 50% drop in baseline MADRS) are removed from the trial. Those not responding (< 50% drop in baseline MADRS) receive a second ARP-like placebo for two weeks. If subjects still do not respond (< 50% drop in baseline MADRS), they receive three types of baseline imaging (fluorodopa positron emission tomography [PET], raclopride PET, and BOLD fMRI). All subjects then receive six weeks of ARP augmentation. At the end of six weeks, all subjects receive a repeat series of scans. Correlations between treatment response and dopaminergic brain function are then assessed (linear correlation between response and nonresponse).

**Results:** Though the data is very preliminary, early review of the data suggests a trend towards increased dopaminergic activation in the striatum of subjects responding to ARP augmentation.

**Conclusions:** Additional data, soon to be collected, will clarify the potential role of dopamine in ARP antidepressant augmentation. Supported by Bristol Myers Squibb

478. Increased Treatment Resistance is Associated with Greater Left Prefrontal Cortex Activation during a Verbal Working Memory Task

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**Background:** Depression is associated with impaired cognitive and prefrontal function. Factors describing the severity of depression such as length of depressive episode (LDE) and treatment resistance may independently contribute to the observed impairment.

**Methods:** Forty-five unmedicated, unipolar depressed subjects (mean age 48.9 ± 12.1 yrs) underwent a verbal working memory, n-back, task in a 3T fMRI scanner at one site (MUSC) in a more encompassing 4-site TMS clinical trial. Treatment resistance was measured with the Antidepressant Treatment History Form (ATHF) and depression was quantified with the Hamilton Rating Scale for Depression (HRSD). Using FMRIB Software Library (FSL) 5.98, we performed a weighted group average, investigating the effects of performance, ATHF score, and ln (LDE in weeks) on mean brain activity during the n-back task.

**Results:** Patients were moderately treatment resistant with average LDE = 62.0 ± 60.5 weeks, HRSD = 27.4 ± 4.8 and ATHF = 2.3 ±1.6. There were no significant differences in performance accuracy that could be accounted for by depression severity or increased cognitive load. Subjects showed predicted bilateral activation of the mid-lateral prefrontal cortex and parietal cortex. The left prefrontal cortex (LPFC) showed increased activation in subjects with higher ATHF scores. Performance and LDE did not uniquely contribute to activation.

**Conclusions:** As expected, the n-back task engages a distributed fronto-parietal network. Subjects with higher treatment resistance had increased activity in the LPFC while achieving behavioral performances equal to less treatment resistant subjects. These patients may be ‘overcompensating’ for a prefrontal deficit associated with higher treatment resistance. Supported by R01MH069886; R01MH069887
479. Neuronal Correlates of Emotional Conflict in Women During Menopausal Transition

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Background: Several prospective studies have demonstrated that women are at higher risk to develop depression during the transition to menopause, a period characterized by wide fluctuations of gonadal steroids such as estrogen and progesterone. Recent studies have revealed that these hormones may modulate brain activity of areas associated with mood regulation. In this study, functional MRI was used to investigate brain activation during an emotional regulation task in a well-characterized sample of women during the menopausal transition.

Methods: Thirteen peri/postmenopausal women (mean age ± SD= 50.1 ± 5.2) were assessed for menopause-related symptoms according to the psychological, somatic and vasomotor symptoms sub-scores of the Greene Climacteric Scale (mean total scores ± SD= 7.4 ± 4.1). Participants performed a standardized task that assesses monitoring and resolution of emotional conflict. Blood-oxygen-level-dependent images were acquired on a 3T GE scanner and haemodynamic contrasts were calculated using Brain Voyager software.

Results: Resolution of emotional conflict was associated with robust engagement of the fronto-limbic network, including rostral anterior cingulate cortex, dorsolateral prefrontal cortex, anterior insula and parahippocampal gyrus (all p<0.05, FDR corrected for multiple comparisons).

Conclusions: Examining brain activation in women during menopausal transition may help to uncover the mechanisms underlying the susceptibility for developing depressive and somatic symptoms during this at-risk period. Supported by CIHR, Father Sean O’Sullivan Research Centre, Eli Lilly and Wyeth Pharmaceuticals.

480. T2 Relaxometry in Pediatric Bipolar Disorder

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Background: Transverse relaxation time (T2) imaging provides the opportunity to examine membrane fluidity, with increased T2 reflecting decreased membrane fluidity. The objective of the present work was to examine T2 in the cingulate-paracingulate (CPC) white matter of children with BD.

Methods: All of the subjects were recruited through McLean Hospital and the Cambridge Health Alliance (outpatient, partial, and inpatient programs). All of the subjects with BD in this study meet criteria for BD I, the intermediate phenotype. After the study was described, all of the parents signed a written informed consent form and the children an assent form. Any adult subjects signed their own consent form. The T2 on the right hand side of the age and sex matched subjects with BD was significantly lower than in the HCS (13.1±3.2years, 7female) (p < 0.003). Six age and sex matched subjects were identified to compare T2 relaxometry and Diffusion Tensor Imaging (DTI) data were acquired on a GE 1.5 T MRI scanner using the methods of ref1 and ref2. Results: The T2 on the right hand side of the age and sex matched subjects with BD (13.1±3.2years, 7male) was significantly lower than in the HCS (13.2±2.9years, 7female) (p < 0.003). Six age and sex matched subjects were identified to compare FA, trace diffusivity and T2 values: the trace diffusivity was higher in both the right (p < 0.008) and left PCP compared (p < 0.03) with the HCS.

Conclusions: Diminished reward-related DA signals in depression/schizophrenia could relate to anhedonia/negative symptoms, and also to psychotic symptoms by contributing to abnormal associations.

Methods: Depression, schizophrenia and a control groups, were scanned using fMRI during an instrumental reward-learning task. A TD model was used to generate a reward-learning signal that was used for image analysis.

Results: Depressive patients demonstrated reduced TD signals in the midbrain and striatum compared to controls. Schizophrenic patients demonstrated reduced activation in the upper caudate, insula, amygdala and hippocampus compared to controls and increased activation in the striatum compared to depressed patients. In schizophrenia, decreased activation in the midbrain and insula correlated with increased severity of psychotic symptoms.

Conclusions: Diminished reward-related DA signals in depression/schizophrenia are consistent with anhedonia/negative symptoms. In schizophrenia, abnormal DA signals may be associated with psychotic symptoms by attributing aberrant salience to stimuli. In the striatum, abnormalities in DA signals seem more marked in depression than in schizophrenia. These results may help to bridge the gap between the biology and phenomenology of the illnesses and highlight the potential role of abnormalities of phasic signals as biomarkers of psychiatric disorders.

Supported by SINAPSE, Miller McKenzie Trust, Scottish Office.

481. Abnormal Reward Prediction Error Signals in Depression and Schizophrenia

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Background: Abnormal functioning of the dopamine (DA) system has been linked to anhedonia in depression and negative plus positive symptoms in schizophrenia. It remains unclear though, how a DA dysfunction could mechanistically link to symptoms. “Phasic” DA signals code a reward prediction error that may mediate learning of stimulus-response-outcomes associations and/or attribution of incentive salience to stimuli. Temporal difference (TD) models provide a mathematical description of these signals. Abnormalities of DA signals in depression/schizophrenia could relate to anhedonia/negative symptoms, and also to psychotic symptoms by contributing to abnormal associations.

Methods: Depression, schizophrenia and a control groups, were scanned using fMRI during an instrumental reward-learning task. A TD model was used to generate a reward-learning signal that was used for image analysis.

Results: Depressive patients demonstrated reduced TD signals in the midbrain and striatum compared to controls. Schizophrenic patients demonstrated reduced activation in the upper caudate, insula, amygdala and hippocampus compared to controls and increased activation in the striatum compared to depressed patients. In schizophrenia, decreased activation in the midbrain and insula correlated with increased severity of psychotic symptoms.

Conclusions: Diminished reward-related DA signals in depression/schizophrenia are consistent with anhedonia/negative symptoms. In schizophrenia, abnormal DA signals may be associated with psychotic symptoms by attributing aberrant salience to stimuli. In the striatum, abnormalities in DA signals seem more marked in depression than in schizophrenia. These results may help to bridge the gap between the biology and phenomenology of the illnesses and highlight the potential role of abnormalities of phasic signals as biomarkers of psychiatric disorders.

Supported by SINAPSE, Miller McKenzie Trust, Scottish Office.

482. Urinary Oxytocin is Related to Mothers’ EPDS Scores, Neural Response to Infant Images and Feeding Method

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Background: Oxytocin (OT) is related to affect and social affiliations. We investigated the association between urinary oxytocin (OT), postpartum depressed mood, infant feeding method and mothers’ neural responses to video of their own infants.

Methods: New mothers, tested at 1-3 months postpartum (25 Breast-, 11
Formula-feeders), underwent a lab session of maternal stress, mother-infant interaction, and feeding. Urine for OT assay, and visual analog scale ratings of irradiation and sadness were collected before and after each event. The Edinburgh Postnatal Depression Scale (EPDS) was used to assess depressive symptoms. On another day mothers completed an fMRI protocol consisting of 15-segment video clips of their Own infant and a matched Other infant, presented in block design. OT levels were measured with EIA (Assay Designs). fMRI data was collected on a 3T Siemens Allegra scanner, and processed with FSL and FEAT (FMRIB, Oxford).

**Results:** OT was correlated with lower EPDS scores ($r = -.55$), and ratings of sadness and irradiation following infant contact. Higher OT was linked to greater fMRI BOLD response to Own infant in bilateral orbital frontal, medial PFC, DLPFC, striatum, and right posterior superior temporal gyrus ($Z > 2.3$). Greater OT, lower EPDS, and greater BOLD response to Own infant in frontal cortex was seen in Breast-compared with Formula-feeding mothers.

**Conclusions:** Breastfeeding may contribute to mother-infant attachment by enhancing neural activation to infant cues and reducing negative affect during infant interactions. Supported by K01DA099949; P01DA022446; R01HL084222

### 483. The Modulation of Fear and Empathy Processing by Oxytocin- A fMRI Study in Healthy and Depressed Subjects

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**Background:** In healthy subjects Oxytocin (OT) administration reduces activation of the amygdala and coupling of the amygdala to brainstem regions in response to fearful stimuli. There seems to be an association between plasma-OT and severity of depressive symptoms, but the effect of OT on fear response and amygdala reactivity in patients with major depressive disorder (MDD) has not been investigated yet. A disturbance in empathy in MDD patients might be related to the decoupling of modulatory processes, which could be partially based on a deregulated OT effect. While in healthy subjects OT increases trust in interpersonal interactions and the ability to infer the mental state of others, its effects on these processes in MDD have not been investigated yet.

**Methods:** Neural activity during fear- and empathy-related processing was investigated using functional magnetic resonance imaging (fMRI). 20 patients and 20 controls were investigated after double-blind administration of placebo or OT.

**Results:** Patients with MDD showed abnormal signal changes in the fear circuit and the prefrontal cortex as well as a correlation of depression severity with altered signal changes. In healthy subjects, the administration of OT reduced fear as well as empathy, while in MDD a differential effect on fear and empathy was observed.

**Conclusions:** The effect of OT on fear and empathic abilities due to an alteration of responses in the amygdala and prefrontal cortex contributes to the understanding of the pathophysiological mechanisms of emotional symptoms in MDD and their possible therapeutic manipulation by OT administration.

### 484. Lithium Shows Large Positive Effect on Dorsolateral Prefrontal Cortex N-acetyl Aspartate in Bipolar Patients

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**Background:** Converging lines of evidence suggested neuroprotective effects of lithium. N-acetyl aspartate (NAA) can be used for in vivo testing of such effects. Previous studies of NAA in lithium treated subjects showed mixed results due to differences in dosage, duration and monitoring of lithium treatment.

**Methods:** We recruited 23 patients from specialized lithium clinics in Berlin and Halifax, with at least 2 years of regularly monitored lithium exposure (Li group), and compared them to 13 subjects with less than 3 months lifetime lithium exposure >2 years ago (non-Li group) and 21 healthy controls. Both patient groups had at least 10 years illness duration and were euthymic at the time of scanning. We measured NAA levels from dorsolateral prefrontal cortex (DLPFC) using 1.5T magnetic resonance spectroscopy. The effect sizes (Cohen’s d) for NAA differences between groups in individual sites were combined using random effect models.

**Results:** The non-Li group had significantly lower NAA levels than Li group d=-1.30 (95%CI=-2.05,-0.55) and controls d=-1.05 (95%CI=-1.81,-.0.28), with no difference between Li group and controls d=0.06 (95%CI=-0.53, 0.66). The same pattern of NAA in Li group<controls>non-Li group, was independently replicated in both sites.

**Conclusions:** Whereas patients with <2 months of lifetime lithium exposure had significantly lower NAA in DLPFC, patients with the same duration of illness, but with >2 years of lithium exposure showed NAA levels comparable to healthy controls. The effect size for the difference between lithium treated vs. untreated subjects was large (ES=1.3). These results provide in vivo evidence for neuroprotective effects of lithium.

Supported by the International Group for The Study of Lithium Treated Patients, Dalhousie Clinical Research Scholar Award to Dr. Hajek

### 485. The Long-Term Neuroanatomical Impact of Childhood Emotional Maltreatment

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**Background:** Childhood emotional maltreatment (CEM) has been associated with a profound and enduring negative impact on behavioral and emotional functioning. Recent studies have shown that CEM is particularly associated with maladaptive emotional functioning in adulthood which may increase the risk for the development of psychiatric disorders when faced with stressors in later life. However, the neurobiological correlates that may serve to explain this emotional vulnerability in individuals reporting CEM are yet unknown.

**Methods:** We used high-resolution T1-weighted 3T MRI anatomical scans to examine whether adults (unmedicated patients with depression and/or anxiety disorders, and healthy controls) reporting CEM before the age of 16 ($n=84$,...
mean age=38.7) displayed structural brain changes on brain regions that are involved in emotion processing and regulation (i.e., amygdala, hippocampus and medial prefrontal cortex) in comparison to patients and controls who did not report a history of childhood abuse (n=97, mean age=36.6).

**Results:** Self-reported CEM, which occurred at least regularly, was associated with a 7.2% reduction in left dorsal medial prefrontal cortex (dmPFC) gray matter volume, in males and females, independent of psychopathological status.

**Conclusions:** In this study, we show that CEM is associated with a profound and long-lasting impact on mPFC morphology, suggesting that sustained inhibition of growth, or even structural damage, can occur after exposure to CEM. Given the important role of the mPFC in the regulation of emotional behavior and physiological stress responses, our finding may represent an important missing link in understanding the increased emotional sensitivity in individuals reporting CEM.

**486. Pre-Operative Resting State Functional Connectivity is Associated with Intraoperative Response to Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression**

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**Background:** Subcallosal cingulate (SCC) deep brain stimulation (DBS) is associated with an acute intraoperative response in roughly two-thirds of patients with treatment-resistant depression (TRD). These effects predict 1- and 6-month antidepressant effects with chronic stimulation. We performed a baseline resting state functional magnetic resonance (fMRI) functional connectivity (FC) analysis to determine if pre-operative network state was different between patients with (IOR) and without (nIOR) an intraoperative response to SCC DBS.

**Methods:** TRD patients (N=11) underwent fMRI scanning prior to DBS surgery. Intraoperative testing identified 7 IOR and 4 nIOR subjects. For each subject, the average fMRI time series of an SCC seed (at the site of the implanted electrode) was correlated with that of all other brain voxels. FC maps were Fisher z transformed and compared between the IOR and nIOR groups using independent samples t-tests with results thresholded at p<0.005 and a minimum cluster size of 8 original space voxels.

**Results:** Pre-operative SCC FC showed differential connectivity with right frontal pole and left dorsolateral prefrontal cortex in IOR vs. nIOR patients. Specifically, IOR patients showed little correlation between these regions, where nIOR patients showed a negative correlation.

**Conclusions:** Acute intraoperative effects of SCC DBS have important short-term clinical implications. These findings suggest that the pre-operative state of a mood regulation network may predict which patients are more or less likely to experience these effects. By using resting state fMRI for FC analyses, there is the potential to develop a patient-level indicator to assist with SCC DBS treatment planning.

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**487. Atlas-Based Segmentation of White Matter in Major Depressive Disorder Using DTI Collected as Part of Routine Clinical Treatment**

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**Background:** A few diffusion tensor imaging (DTI) studies have shown abnormalities in areas of white matter (WM) tracts involved in mood regulation using techniques based on voxel-based morphometry or regions-of-interest. However, these studies are restricted to single fiber tracts or require perfect alignment. In this study, we explored whole brain WM in major depressive disorder (MDD) by registering a WM atlas onto subjects’ brains. Our neuroimaging (DTI) data had been collected previously as part of routine clinical treatment.

**Methods:** We screened electronic medical records and found 95 MDD subjects with coexisting DTI data and 33 age and gender-matched controls with no history of neurological or psychiatric illness. A hand-segmented white matter atlas-based segmentation method with DTI that was collected as part of routine clinical treatment. Our neuroimaging (DTI) data had been collected previously as part of routine clinical treatment.

**Results:** Regionally, depressed patients showed significantly reduced FA of the body and column of the fornix (p<.045). MDD subjects with non-remitted depression had lower FA in the fornix than MDD subjects in remission and healthy volunteers (p<.05). From the whole brain perspective, depressed patients had non-significant but lower FA on 19/23 fronto-temporal and long association WM tracts (p<.002, X<9.8 for the group analysis).

**Conclusions:** In this study we successfully used an atlas-based WM segmentation method with DTI that was collected as part of routine clinical treatment. Our findings suggest both regional and global white matter abnormalities in MDD.

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488. Acute Tryptophan Depletion Increases Cingulate Cortex Reactivity inRecovered Depressed Patients - An fMRI Investigation

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Background: Acute tryptophan depletion (ATD) reduces serotonin levels. Behaviourally, low dose ATD increased interference effects in an emotional Stroop task in recovered depressives. Horacek et al and Evers et al showed using fMRI that ATD increases neural response to conflict in Stroop tasks in healthy volunteers. However, no neuroimaging studies have examined the effects of ATD during the Stroop task in recovered depressives.

Methods: We recruited 21 currently unmedicated, recovered depressed patients. Subjects were assigned to low-dose (31.5g) ATD amino acid drink, or balanced drink containing tryptophan as a placebo control. We used a randomized, double-blind, parallel-groups design. A lexical counting Stroop task was used. Words were positive, neutral, socially threatening e.g. “humiliated” and physically threatening e.g. “injury” vs. fixation cross baseline. We also measured resting-state brain haemoperfusion using arterial spin labeling (ASL) MRI.

Results: As expected, low-dose ATD had no mood effects, but ATD increased neural activity in the Stroop task in a cortical midline network including the posterior cingulate and the anterior cingulate (ACC) (whole-brain fully corrected, thresholded Z>2.3 cluster significance P<0.05). These changes were seen in the absence of differences in resting-state haemoperfusion.

Conclusions: Low-dose ATD increased cortical midline (including ACC and PCC) responses to conflict in a Stroop task. This finding is consistent with earlier reports of increased ACC reactivity with ATD in healthy volunteers, and extends them to recovered depressives. Interestingly, this suggests that 5HT depletion produces similar neural effects in healthy and recovered depressed subjects, despite different mood effects at high doses.

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489. Neurobiological Markers of Bipolar Disorder: Evidence from Two Neuroimaging Meta-Analyses

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Background: Identifying objective biomarkers, such as functional and structural brain abnormalities in patients with bipolar disorder, is needed. Our objective was to identify neurobiological markers of bipolar disorder through two meta-analyses of first, functional neuroimaging studies related to emotional processing in bipolar disorder and second, of structural whole-brain neuroimaging studies.

Methods: Only studies comparing patients with bipolar disorder to healthy comparison subjects were considered. Functional magnetic resonance imaging studies were included if they investigated the neural correlates of emotional processing, structural magnetic resonance imaging studies if they used voxel-based morphometry. Twenty-five studies involving a total of 506 patients and 603 healthy controls were included (13 for functional imaging and 12 for structural imaging). The data were extracted or converted to a single anatomical referential (Talairach space). The activation likelihood estimation technique was used to assess the voxel-wise correspondence of results between studies.

Results: In patients with bipolar disorder decreased activation and diminution of gray matter were identified in a dorsal brain network that has been associated with the regulation of emotions. In contrast, patients with bipolar disorder exhibited increased activation in ventral limbic brain regions that underlie the experience of emotions and the generation of an emotional response.

Conclusions: These meta-analyses provide evidence for neurobiological biomarkers of bipolar disorder in the brain networks subserving the experience and regulation of emotions. The results of a hypoactive and structurally diminished dorsal neural pathway together with a hyperactive ventral-limbic pathway further support previously proposed neurobiological models of bipolar disorder.

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490. Effective Connectivity within the Network of Fearful Facial Affect Recognition in Patients with Bipolar Disorder Compared to Healthy Controls

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Background: There is significant overlap between the cortical network involved in fearful face perception and regional abnormalities identified in patients with bipolar disorder. The primary aim of this study was to measure effective connectivity arising from Dynamic Causal Modelling (DCM) to identify differences within this network in a group of patients with bipolar disorder and controls during an affective processing task.

Methods: Functional MRI was used to record brain activations from 52 euthymic patients with bipolar disorder and 44 healthy controls engaged in a fearful versus neutral facial affect recognition task. We used Bayesian model selection to identify the best model of effective connectivity, as well as a random-effects analysis. Additionally, the endogenous connections and modulatory influences were extracted and further analyzed.

Results: Within the network subserving fearful facial affect recognition, patients with bipolar disorder demonstrated reduced connectivity from the inferior occipital gyrus to the fusiform gyrus compared to healthy controls. Furthermore this connection when modulated by fear showed a reduction in strength in patients with bipolar disorder.

Conclusions: Bipolar disorder was associated with deficits early in the processing of facial affect suggesting the possibility of perceptual abnormalities being associated with the disorder.

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491. Persisting Abnormal Lateral PFC Activation in Remitted Depressed Patients During the Performance of an Emotional Working Memory Paradigm

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Background: This study aimed to examine differences in BOLD fMRI activation of key neural regions supporting attentional control in the context of emotion in recovered depressed patients compared to healthy controls.

Methods: 19 euthymic, medication-free remitted depressed patients (rMDD) (mean age 33.6 ± 13.64) and 20 age-gender matched healthy controls (HC) (mean age 35.8 ± 12.10) underwent an fMRI scan at 3T, during which they performed a novel Emotional Face N-back (EFNBACK) task. Subjects were directed to ignore emotional facial expressions (fearful, happy, or neutral) while performing a visual N-back task (0-back, 2-back). Images were pre-processed using SPM2. Group differences were measured for 2 main contrasts of interest: 2-back fearful versus 2-back neutral and 2-back happy vs. 2-back neutral conditions. For regions of interest (ROI), small volume correction (SVC) analyses were performed. Accuracy and reaction time were also analyzed.

Results: For the 2-back fearful vs. 2-back neutral condition, ROI analyses revealed increased activation in rMDD patients relative to HC in the following regions: ventromedial PFC (BA10/11) [p< 0.008], DLPFC (BA9/46) [p< 0.005] and amygdala [p< 0.02]. In contrast, the 2-back happy vs. 2-back neutral was associated with significantly greater activation in DLPFC [p< 0.01], VLPFC [p< 0.001] and ventral striatum [p< 0.015] in HC relative to rMDD.

Conclusions: rMDD patients continue to display altered neural responses in areas subserving attentional control processes implicated in modulating emotional information. Results suggest differential patterns of activation for negative vs. positive stimuli, which may be indicative of trait-like abnormalities associated with the disorder.

492. Prefrontal Subregional Hemodynamic Response and the Correlation with Symptoms and Functioning in Major Depression: A Multi-Channel NIRS Study

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Background: Major depressive disorder (MDD) is associated with dysfunction of the prefrontal cortex (PFC). We investigated region-specific characteristics of prefrontal activation in patients with MDD using a noninvasive and low constraint functional neuroimaging technique, near-infrared spectroscopy (NIRS). Our goal was to explore an objective neuroimaging biomarker to detect prefrontal functional abnormalities in MDD.

Methods: Thirty two patients with MDD, and 32 age, sex and performance matched normal controls were recruited in this study. The total HDR-S score of all depressive subjects were above 15. Using a 52-channel NIRS instrument (HITACHI ETG-4000), the relative changes of [oxy-Hb] during verbal fluency task over the PFC were compared between the two groups. Clinical symptoms and functioning were also assessed. All the subjects gave written informed consent according to the ethics committee of the University of Tokyo Hospital and JR Tokyo General Hospital.

Results: MDD subjects showed significantly lower [oxy-Hb] increase over PFC regions than control subjects (FDR corrected p < 0.003). [oxy-Hb] changes have significant correlations with the Global Assessment of Functioning (GAF) scores in dorsolateral and ventrolateral PFC regions (FDR corrected p < 0.009).

Conclusions: These results suggest prefrontal functional abnormalities engaged in poor functioning in patients with MDD. Prefrontal hemodynamic response assessed by a noninvasive NIRS may be a potential neuroimaging biomarker for evaluating prefrontal dysfunction in MDD.

493. Underactivation of Cortical-Striatal-Thalamic Circuits in Euthymic Bipolar Patients during Choices to Immediate Monetary Rewards

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Background: The inability to delay gratification and the overvaluation of short-term rewards are key features of the impulsivity seen in Bipolar Disorder (BD). Overvaluation of short-term rewards has been implicated in BD, suggesting dysfunction in the dopaminergic system.

Methods: Based on these considerations, we predicted that BD subjects would show alterations in frontal, limbic, and striatal fMRI activation during performance of a delay discounting task. Twelve adults with type I bipolar disorder, medicated and currently euthymic (YMRS<12, MADRS<12) were recruited from the University of Cincinnati Academic Health Center, along with a demographically-matched group of eighteen healthy subjects. After providing informed consent, all subjects participated in an fMRI session on a 4.0 T Varian Unity INOVA whole-body MRI/MRS system while performing a delay-discounting task. Twelve adults with type I bipolar disorder, medicated and currently euthymic (YMRS<12, MADRS<12) were recruited from the University of Cincinnati Academic Health Center, along with a demographically-matched group of eighteen healthy subjects. After providing informed consent, all subjects participated in an fMRI session on a 4.0 T Varian Unity INOVA whole-body MRI/MRS system while performing a delay-discounting task. Subjects were instructed to choose between a hypothetical immediate or delayed payment of $10 available after a delay (1, 7, 30, or 60 days) or a smaller amount available immediately (0 days).

Results: There were no statistically significant differences in reaction time or delay discounting measures between groups. During choices of smaller immediate rewards, healthy subjects demonstrated significantly greater activation than euthymic patients in bilateral parahippocampal gyrus, bilateral thalamus, bilateral striatum, and medial superior frontal gyrus (BA9). These findings suggest that remitted bipolar patients demonstrate decreased activation in striatal and thalamic regions during short-term reward valuation. Alterations in these striatal and thalamic regions might underlie the overvaluation of immediate rewards and inability to delay gratification seen in bipolar subjects.

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Background: Hippocampal integrity is critical for spatial learning processes. Recent studies using a virtual analog of the Morris Water Maze (vMWM) task showed that spatial navigation elicits hippocampal oscillatory activity in the 4-8Hz (theta) range in humans, and that patients with unipolar depression exhibit impaired navigation performance along with abnormal hippocampal theta activity. However, spatial memory and hippocampal function have not been adequately investigated in patients with bipolar depression (BD). The present study uses the vMWM task to investigate hippocampal theta activity in BD patients during spatial navigation. We hypothesized that BD patients would display impaired spatial navigation performance and reduced hippocampal and parahippocampal theta activity compared to controls.

Methods: We recorded brain activity with magnetoencephalography in nine BD patients and nine healthy subjects while they completed a vMWM task. Path length and heading error were used to measure behavioral performance. MEG data was analyzed using Synthetic Aperture Magnetoetry to estimate the volume distribution of source power across the brain in the theta band.

Results: BD patients performed worse than controls in navigating toward the hidden platform (Group X Condition ANOVA interaction: p = 0.02 for path length and p = 0.10 for heading error). Source analyses indicated a significant decrease in hippocampal and parahippocampal theta activity in BD patients compared to controls during the hidden trials (p<0.01, uncorrected).

Conclusions: This study provides evidence of spatial memory deficits in patients with BD which might be related to impaired hippocampal theta activity.

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495. Enhanced Neural Responses to Interpersonal Feedback in Patients with Major Depression

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Background: Negative interpersonal feedback (criticism) is a commonly encountered stress that has been associated with psychiatric disorders, especially depression. In the present study, we aimed to map the neural correlates of emotional response to interpersonal feedback in patients with major depression as compared to healthy controls.

Methods: Female patients with major depressive disorder based on DSM-IV and age- and sex-matched controls underwent 1.5T fMRI scanning while performing challenge task in presence of interpersonal stress. Subjects solved to puzzles (geometric problem solving), while shown pre-recorded video clips with cues depicting criticism, neutral and approval feedback.

Results: Depressed patients showed activations in anterior cingulate (ACC), right amygdala and both temporal lobe in response to approval relative to fixation condition. Criticism feedback relative to fixation activated both insula, both inferior frontal lobe, both middle frontal lobe, left superior temporal lobe and left parietal lobe. Neutral relative to fixation showed activations in bothinsula, anterior cingulate, both inferior frontal lobe, left superior temporal lobe and left amygdala. Approval relative to criticism feedback activated left amygdala, right anterior cingulate, left caudate, right temporal lobe and precuneus. Criticism relative to approval feedback showed activations in left inferior frontal gyrus (OFC), SMA and paracentral lobule.

Conclusions: Neural responses to interpersonal feedback were enhanced in patients with depression as compared to healthy control. Positive interpersonal feedback showed activations in limbic, reward and appraisal system. In contrast, negative interpersonal feedback enhances BOLD signal in the emotion expression and regulation system

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496. A Magnetic Resonance Imaging Study of the Effects of Antidepressant Treatment on Brain Structure in Major Depressive Disorder

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Background: The majority of the structural MRI studies in major depressive disorder (MDD) focused on the limbic structures, while only a few studies examined the entire brain. There have been little or no information on the effects of antidepressant treatment on the brain’s main structural components. In this study, we examined whether antidepressant treatment is associated with changes in brain structure in patients with MDD.

Methods: A total of 35 patients with MDD and 40 age and sex matched healthy controls were recruited for this study. Seventeen patients had received continuous antidepressant treatment for 26 months and eighteen patients were medication free for ≥12 months. Images were acquired using a 3T scanner, while intracranial volumes (ICV) were segmented manually using DISPLAY. Groups were compared using MANCOVA and post hoc tests.

Results: Groups did not differ in age, sex, education and ICV (all p>0.05). Volumes of gray matter, white matter and cerebrospinal fluid did not differ between unmedicated MDD patients and healthy controls after controlling for ICV (all p>0.05). Medicated MDD patients had significantly larger white matter volume (p=0.048), total brain volume (p<0.01) and smaller cerebrospinal fluid volume (p=0.009) than controls. Gray matter volume did not differ between any groups (p>0.05).

Conclusions: This preliminary cross-sectional study suggests that antidepressants may have an effect on brain structure, particularly on the volumes of white matter and cerebrospinal fluid. Additional longitudinal studies are needed to confirm our findings.

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497. Reduced Neural Response to Reward following 7 Day Treatment with the Cannabinoid CB1 Antagonist Rimonabant in Healthy Volunteers

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Background: Deficits in the neural processing of reward are seen during acute episodes of major depression and during remission. We hypothesised that our neuroimaging reward model would be sensitive to drugs such as the obesity drug and cannabinoid type 1 receptor antagonist, rimonabant which
has recently been withdrawn from the market due to side-effects of depression and anxiety.

Methods: We studied 22 healthy participants who were randomly allocated to receive rimonabant, or placebo for 7 days in a double-blind, parallel group design. We used fMRI to measure the neural response to rewarding (sight and/or flavour of chocolate) and aversive stimuli (sight of mouldy strawberries and/or an unpleasant strawberry taste) on the final day of drug treatment. Volunteers also rated the pleasantness, intensity and wanting for each of the stimuli.

Results: Despite no significant differences between the groups in subjective ratings rimonabant reduced activation to the chocolate stimuli, in key reward areas such as the ventral striatum and the orbitofrontal cortex (p<0.05 whole brain corrected). Rimonabant also decreased neural responses to the aversive stimulus condition in the caudate nucleus.

Conclusions: Our findings are the first to show that treatment with the anti-obesity drug rimonabant can diminish the neural processing of rewarding stimuli. The ability of rimonabant to decrease neural responses to anticipation of reward could be involved in its role in weight loss but also the reports of depression and anxiety. This model may therefore be useful for early screening of novel agents for unwanted effects on anhedonia, reward and depression. Supported by MRC.

498. Imaging the Mechanisms Underlying Vulnerability to Bipolar Disorder

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Background: Bipolar Disorder is highly familial neuropsychiatric condition for which genetic risk variants are continuously being discovered. The neural mechanisms that lead from risk variants to established illness are however unclear.

Methods: In a study of controls, relatives at high risk of bipolar disorder and affected individuals we have sought to examine the effects of genetic risk variants on gray (T1-MRI) and white (DTI) matter structure and brain function (cognition and fMRI). We have examined both net liability as well as particular SNPs

Results: Individuals with risk variants and those at increased genetic liability show altered brain structure, function and connectivity affecting regions involved in emotion processing and mood which have been reately implicated in unipolar and bipolar mood disorder.

Conclusions: Deficits in brain structure and connectivity are likely to confer liability to bipolar disorder and may help to elucidate the mechanisms leading to increased risk and established disorder. Supported by The Health Foundation

499. D2/D3 Receptor Polymorphisms Predict Amygdala and Subgenual Cingulate Reactivity to Positive and Negative Emotional Stimuli.

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Background: Functional neuroimaging studies in human subjects have consistently implicated the amygdala and anterior cingulate cortex in the processing of emotionally salient stimuli. Furthermore, dopaminergic projections from the ventral tegmentum are known to modulate activity in these regions via D2/D3 receptors. We hypothesized that polymorphic variation in D2/D3 receptor genes would affect activation in amygdala and subgenual cingulate during a task of emotion processing.

Methods: Eighty healthy subjects underwent functional MRI as they read positive, negative, and neutral affective words. Single nucleotide polymorphisms (SNPs) in DRD2 and DRD3 genes were determined using the NIH Addiction microarray. ANOVAs conducted in SPM5 were used to determine statistically significant effects of SNPs on activation in amygdala and anterior cingulate (uncorrected, p < 0.001).

Results: Significant effects were found for SNPs in DRD3 (rs67770) and DRD2 (rs4648318). Compared to GG homozygotes, carriers of the DRD3 A allele showed greater amygdala activation to positive and negative words. Compared to AA and GG homozygotes, AG heterozygotes at the DRD2 locus showed greater activity in subgenual cingulate and amygdala in response to negative words.

Conclusions: Thus, variation in DRD2 relates to processing of aversive information, while variation in DRD3 influences processing of both positive and negative information. It remains unknown whether these polymorphisms are functional, but these results provide evidence that individual variation in dopaminergic modulation of the amygdala and subgenual cingulate may underlie differences in emotional processing. Through this mechanism, variation in dopaminergic neurotransmission might influence vulnerability for affective and anxiety disorders.

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500. Neural Responses to Affective Stimuli are Modulated by NPY Genotype

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Background: Improved prevention and treatment of affective disorders will depend on discovery of novel endophenotypes associated with vulnerability and resilience. Neuropeptide Y (NPY) is a peptide neurotransmitter that is thought to promote resilience to stress. Recent analysis of a haplotype-based functional NPY polymorphism demonstrated that low NPY expression is associated with greater anxiety, increased amygdala responses to threat, and decreased endogenous μ-opioid responses to pain. We hypothesized that low-expression NPY genotypes would be associated with more negative self-reports of affect, and greater neural responses to negative affective stimuli.

Methods: Affect experiment. Ninety-six healthy adults completed a study of experimental pain-stress. Subjects provided self-reports of affect immediately before and after the stress challenge. Imaging experiment. Seventy healthy adults participated in an fMRI study in which they viewed emotionally-valenced words. The BOLD response was quantified for negative versus neutral words. Genotyping. Haplotypes were constructed from 6 markers near the NPY gene and subjects were classified according to haplotype-predicted NPY expression.

Results: Affect experiment. Lower predicted expression of NPY was associated with more negative self-reports of affect both before and after the pain-stress challenge (p < 0.05, linear regression). Imaging experiment. Task-related activation was found in medial prefrontal cortex. Hemodynamic responses within this region correlated inversely with predicted NPY expression (p = 0.028, linear regression). Whole-brain voxel-level regression further demonstrated an effect of NPY genotype in right rostral anterior cingulate cortex (uncorrected p < 0.001; cluster size, 138 voxels). The low-expression group showed activation in this region, whereas the high-expression group showed deactivation.

Conclusions: These results support our hypothesis that low-expression NPY genotypes are associated with more negative affect and exaggerated
neural responses to negative stimuli. The findings extend previous work by implicating key cortical regions involved in affective processing. Gene-associated variation in affective processing in prefrontal and anterior cingulate cortices may represent a risk endophenotype for affective disorders.

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501. Investigation of High Energy Metabolism in Lithium Treated Children with Bipolar Disorder: A 31P MRS Study

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Background: A number of studies have suggested that Bipolar Disorder (BD) may be a disorder of high-energy-metabolism, that is involving mitochondria. Using in vivo 31P MRS it is possible to measure high-energy-phosphate metabolites.

Methods: Subjects were recruited through McLean Hospital. Diagnosis of BD, or not, was confirmed using the KSADS-PL administered by a psychiatrist who works routinely with children. 31P MRS data were acquired on a 4.0 T magnet using methods previously described (Forester et al, NMR in Biomedicine 2009).

Results: To date fourteen subjects participated in this study; 8 subjects with BD (16.8±2.5years, 4female, YMRS: 10.2 ± 9.8) and 6 healthy-comparison-subjects (HCS: age 14.5±5.2years, 4female). All of the subjects with BD were receiving psychiatric medication: all but one were treated with lithium. MANOVA was performed to examine the group differences between inorganic phosphate (Pi), b-ATP, pH and phosphocreatine (PCr). Pi was significantly lower in the subjects with BD compared with HCS (F=11.02, p<0.006). In addition, pH was inversely correlated with the YMRS in the subjects with BD (R2=0.6, F=9.28, p<0.02).

Conclusions: Reduced Pi is consistent with the hypotheses that impaired energy production is involved in BD. While these results do not replicate the findings of others (reduced PCr and pH) in subjects with BD) we did note a significant association between lower levels of pH and higher YMRS. However, all of the subjects with BD treated in this study were receiving psychiatric medications, in particular lithium. Yildiz,Moore et al (2005) have measured reduced Pi after two weeks of lithium treatment in healthy adults.

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502. Altered Reward Anticipation in Youth At-Risk for Depression Following Winning, Losing, and Neutral Outcomes

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Background: Motivational systems, including anticipation of reward, appear to be altered in youth with depressive disorders and have been proposed to be altered in individuals at-risk for developing these disorders. Behavioral and self-report methods find decreased motivation for reward-related behavior following disappointment in at-risk youth. In the present study, we examine the possibility that reward-anticipation-related brain function in the striatum is reduced following loss compared to following win in youth at-risk for developing major depressive disorder.

Methods: Ten youth with a familial history of depression (at-risk) and 17 youth with no family history of depression (low risk) participated in a functional magnetic resonance imaging study on a 3T Siemens Allegra scanner using a matching game with monetary reward. At-risk and low-risk groups were compared for striatal response to anticipation of reward following winning, non-winning, losing, and non-losing trials using SPM5.

Results: Analyses found a significant interaction between risk status and previous-trial outcome in predicting striatal function during reward anticipation \(F(3,100) = 9.28, p<0.01\). Follow-up analyses found that at-risk youth demonstrated significantly greater striatal activation following non-winning \(t = 3.39, p < .01\) and losing trials \(t = 2.89, p < .01\) than low-risk youth.

Conclusions: Rather than the expected reduced striatal reactivity after wining and non-losing outcomes, at-risk youth demonstrated significantly greater striatal reactivity following non-winning and losing trials. This may suggest difficulties modulating striatal response to different outcomes and could represent a progression of altered striatal reactivity from at-risk periods to clinically depressed states.

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503. A Voxel Based Morphometry (VBM) Study of Adolescent Offspring with High Family Loading for Major Depressive Disorder

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Background: Emerging evidence suggests that subjects with MDD as well as offspring of MDD subjects prior to expression of the illness display reduced cortical volume. We expect decreased cortical volume in MDD offspring compared to offspring of unaffected subjects (LR).

Methods: We assessed 152 adolescents, ages 12 - 15 years, with at least one first- and second-degree relative with depression who did not meet criteria for bipolar disorder or depression (MDD-HR). These subjects were compared with 164 low-risk adolescents (LR) who had no family members with mood disorders. Family members were assessed with the Family History Interview (FHI), while adolescents were assessed using the K-SADS -PL. A three dimensional MRI was obtained on a 3T scanner and VBM analyses were conducted using Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) tools. We compared regions of interest using ANOVA with age and gender as covariates. We used an alpha of \(p \leq 0.001\) to correct for multiple comparisons.
Results: We did not find any difference in cortical volume between our two groups using our a priori level of significance. We did find trends for decreased cortical volume in the MDD-HR group in the left anterior middle temporal gyrus (p = 0.003), the right (p = 0.004) and left (p = 0.003) posterior inferior temporal gyrus and the left anterior supramarginal gyrus (p = 0.003). See Table 1, Figure 1.

Conclusions: Our findings suggest subtle morphological differences in adolescents at risk for mood disorder prior to the onset of illness.

504. Neural Predictors of Depressive Relapse Following Cognitive Therapy
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Background: Depression is a common and debilitating mental disorder. Although cognitive therapy (CT) is an effective short term treatment for depression, post-CT relapse is common. In order to understand why relapse occurs, it is potentially useful to examine its neural basis. Neural activity in response to idio graphically generated, self-relevant negative words may provide a clinically meaningful predictor of relapse severity.

Methods: Unmedicated depressed individuals (N = 12) underwent BOLD fMRI assessment while rating the personal relevance of words using a slow-event related design (GE 3T, reverse spiral pulse sequence). Afterward, depressed participants completed 16 sessions of CT, then completed 2-34 months of follow-up assessments. Whole-brain voxelwise regressions of relapse severity on mean fMRI signal 6-10.5 seconds after presentation of idiographically generated negative, self-relevant words minus a prestimulus baseline were used to detect regions in which activity was associated with relapse, subject to empirically determined contiguity thresholding to control type I error.

Results: Individuals whose sustained activity in response to negative words was high in the right insula (Brodmann area 13) demonstrated the strongest relapse severity (Rsq = .48, p<.005, 24 voxels in the cluster).

Conclusions: The insula is associated with interoceptive awareness. Thus, these preliminary data could suggest that CT is associated with the greatest long-term benefits for individuals who process negative, self-relevant information cognitively or intellectually rather than viscerally. More viscerally oriented individuals may require more sustained treatment or other adjunctive treatments following CT.

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505. Neural Markers of Early Treatment Response During Antidepressant Treatment in Major Depressive Disorder
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Background: Neural markers of early treatment response would be useful for effective treatment and drug development in MDD. We evaluated the neural predictors and correlates of early treatment response during the first week of antidepressant treatment in MDD using functional magnetic resonance imaging (fMRI).

Methods: 19 patients with MDD were scanned at the pre-treatment baseline (T1) and one week (T2) during the course of double-blind randomized control treatment with citalopram (20mg) or seroquel XR (150-300mg). While in the scanner, patients performed emotional face matching task of negative (fear, anger, sad) and happy faces and control task of geometrical designs. Based on a previous Meta-analysis, a 20% reduction in HAM-D 17 items scale at week one from the baseline was considered as early response.

Results: There were no differences in age, sex and baseline HAM-D scores between early responders (N=9) and non-responders (N=10). Early responders in contrast to non-responders exhibited increased pre-treatment activation in left subgenual cingulate, inferior frontal and temporal cortices to negative faces. Furthermore, in comparison between T2 and T1, responders revealed activation in right anterior cingulate cortex (ACC) and temporal regions and the non responders showed activation in right visual cortices and left orbito-frontal areas to negative facial stimuli.

Conclusions: The subgenual cingulate and inferior frontal activation to negative facial stimuli predict early treatment response and dorsal ACC responses indicate early improvement to antidepressant treatment. These findings complement extant models that emphasize the reciprocal interactions of subgenual and dorsal ACC network in clinical improvement with antidepressant treatment.

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506. Mirtazapine Reduces Neural Responses to Fearful Faces in Healthy Volunteers
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Background: Previous studies suggest monoamine reuptake inhibitors alter emotional processing in healthy volunteers. It is unknown, however, if these changes are common to all antidepressants with differing pharmacological actions. Mirtazapine is a clinically established antidepressant. Its complex actions involve the blockade of monoamine receptors including noradrenaline.

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α2-adrenoceptors and several 5 HT receptors. This study investigated the effects of a single dose of mirtazapine on neural processing of emotional faces using fMRI in healthy volunteers.

Methods: Twenty-eight volunteers received a single dose of mirtazapine (15mg) or placebo after which they underwent an fMRI scan in which neural responses to implicitly processed fearful and happy facial expressions were assessed.

Results: Whole brain analysis revealed decreased response under mirtazapine to fearful versus happy faces in two brain regions implicated in affective processing. Mirtazapine attenuated activation to fearful faces in the right temporal cortex (including hippocampus and amygdala) (Z=2.87, p<0.05) and frontal-striatal region (including caudate and orbital frontal cortex) (Z=3.07, p=0.05). Post-hoc analysis of percent BOLD signal change showed decreased responses in both regions under mirtazapine for fearful faces and increased responses for happy faces (all p<0.05).

Conclusions: A single dose of mirtazapine reduces neural responses to fearful faces and increases neural responses to happy faces in the amygdala-hippocampal and frontal-striatal regions in healthy volunteers. These results suggest that mirtazapine affects neural measures of emotional processing in regions implicated in depression and anxiety early in treatment. Such effects may provide a useful biomarker for the development of novel candidate treatments for these disorders.

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507. Regional Brain Gray Matter Volume Differences in Patients with Major Depressive Disorder and Patients with Bipolar Disorder Compared to Healthy Controls as Assessed by Voxel-Based Morphometry

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Background: Currently available evidence suggests there are both overlapping, and distinct abnormalities in brain structure between patients with major depressive disorder (MDD) and patients with bipolar disorder (BD).

Methods: Using voxel-based morphometry (VBM) we investigated the brain structure of 24 inpatients with unipolar depression, 22 inpatients with bipolar depressive, manic or mixed episode, and 42 healthy controls matched for age, gender and years of education.

Results: Patients with unipolar depression exhibited a significant decrease in gray matter volume bilaterally in the structures of ventral striatum (including putamen and caudate), hippocampus, amygdala, thalamic medio-dorsal nucleus and hypothalamus compared to healthy controls. Additionally, there was less gray matter volume bilaterally in the superior posterior and prepyramidal cerebellar lobule. The left insula demonstrated a region of significant gray matter volume increase. Gray matter volume in the posterior cingulate showed a trend for positive correlation with the duration of depressive episodes over the entire disease time span. The direct comparison between bipolar patients and controls did not reveal any significant changes. There was a non-significant trend towards decreased gray matter volume in the area of the right posterior insula and gray matter volume increase in the left motor cortex. Gray matter volume in the right dorsolateral prefrontal cortex, the left angular gyrus and cerebellar vermis showed a positive correlation with the duration of manic episodes over the entire disease time span.

Conclusions: MDD and BD are associated with distinct volumetric gray matter changes. Results are discussed in a disease-specific neuroanatomical context.

508. Hypomanic Experience is Associated with Increased dlPFC and ACC Activity to Socially-Threatening Words

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Background: Bipolar disorder (BD) is associated with abnormalities in brain circuits involved in emotional processing and cognitive control. Previous studies showed altered activity in dorsolateral prefrontal cortical (dlPFC) and anterior cingulate cortical (ACC) regions during an emotional Stroop task. Changes in emotional processing persist in periods of euthymia, however, it remains unclear whether these abnormalities represent long-term vulnerability markers for BD that may be apparent in at-risk individuals.

Methods: High scores on the Mood Disorder Questionnaire (MDQ) may identify those at a continuum of risk for bipolar diagnosis. This study investigated 22 students scoring highly (≥7 mood-elevation symptoms) on the MDQ and 20 low-scoring controls. We used the emotion counting Stroop with concurrent fMRI. Positive, neutral, socially-threatening and physically-threatening words were presented in a block design.

Results: Whole-brain analyses revealed significantly greater right dlPFC activity to socially-threatening vs. neutral words in high MDQ students compared to low-scoring controls (clusters determined by Z>2.0 with corrected significance threshold of p<0.05). In a region of interest analysis of the ACC, the high MDQ students also showed increased neural responses to the same contrast (group x emotion: F(1,40)=8.153, p=0.007; group: F(1,40)=0.095, p=0.760; emotion: F(1,40)=30.045, p<0.001).

Conclusions: High MDQ students showed increased dlPFC and ACC activity to socially-threatening vs. neutral words during a task requiring cognitive control. Such effects may represent vulnerability markers for BD that may contribute to hypomanic experience in the high MDQ group.

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Background: MAO-A inhibitors are effective antidepressants that raise levels of three monoamines in contrast to the selective serotonin reuptake inhibitors (SSRI) which raise levels of one monoamine. However, there has been limited development of MAO inhibitors relative to the development of SSRI. This is the first study to measure brain MAO-A occupancy after six weeks of treatment in depressed subjects with a clinically effective dose of a selective MAO-A inhibitor. This is also the first study to measure brain MAO-A occupancy after repeated administration of St. John’s Wort (SJW), a herb purported to have MAO-A inhibitor properties.

Methods: Thirty-eight [11C]-harmine positron emission tomography (PET) scans were conducted. 19 subjects enrolled in one of three conditions: pre/ post treatment with moclobemide (300 mg bid), SJW (600 mg bid) or test/retest condition. MAO-A VS, an index of MAO-A density, was measured in prefrontal, anterior cingulate, anterior temporal cortex, putamen, thalamus, midbrain, and hippocampus.
Results: MAO-A VS was significantly decreased throughout all brain regions after moclobemide-treatment in comparison to either the test-retest group or the SJW group (mean occupancy of moclobemide treatment: 80 % (sd=10)). SJW treatment did not significantly alter MAO-A VS.

Conclusions: For development of new MAO-A inhibitors, 80 per cent occupancy at steady state dosing is desirable. The magnitude of MAO-A blockade during treatment with moclobemide exceeds the rise of MAO-A binding during illness by more than 40 per cent suggesting that the magnitude of treatment effect during a six week treatment for this target should exceed the disease effect. Supported by Canadian Institutes of Health and Research

510. Wisconsin Card Sorting Test, TEMPS-A Inventory and Polymorphisms of 5HTT, BDNF and DAT1 Genes in Patients with Obesity

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Background: The aim of our study was to assess the temperament, symptoms of depression and frontal dysfunctions in relation to polymorphisms of 5HTT, 5HT2A, 5HT2C, BDNF and DAT1 genes in 500 patients with pathological obesity (BMI>40) in comparison with healthy matched controls.

Methods: Polish version of TEMPS-A inventory was used for evaluation of five dimensions of temperament (depressive, cyclothymic, hyperthymic, irritable and anxious). The intensity of depressive symptoms was assessed with the Beck Depression Inventory. Frontal functions were evaluated with the Wisconsin Card Sorting Test (WCST). Genotypes were assessed with RFLP or VNTR methods.

Results: Prevalence of depressive symptoms in subjects with obesity (50% cases) was remarkably higher than among controls. Patients performed significantly worse on WCST than healthy subjects. Patients had significantly higher scores for depressive, anxious and cyclothymic temperament and lower score on irritable scale as compared to control subjects. A known polymorphism of 5HT2C (+795C>T) could not explain the banding pattern observed. This may indicate that a novel polymorphism that may correlate to obesity was found. Significantly higher prevalence of val/val allele of BDNF gene was detected in patients. Worse performance on WCST and higher intensity of depression were associated with I/I allele of s/s polymorphism of 5HTT, G/G allele of 1438G/A polymorphism of 5HT2A and A1/A10 allele of 3’UTR VNTR polymorphism of DAT1.

Conclusions: The results indicate higher prevalence of depression, distinct temperamental profile and prefrontal dysfunctions in patients with obesity. The features may be related to the polymorphisms of BDNF, serotonin and dopaminergic system genes. Supported by Government of Poland, Department of Science grant no NN 402053136

511. Psychotropic Medication Use and Hyponatremia in an Inpatient Population

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Background: Hyponatremia has been associated with all psychotropic drug classes, especially with selective serotonin reuptake inhibitors (SSRI) and carbamazepine. This study examined the use of psychotropic medications and their association with hyponatremia in an acute psychiatric inpatient population.

Methods: This is a retrospective chart review of the patients admitted to the psychiatric inpatient service during the year 2007 at Beth Israel Medical Center, New York. A total of 101 cases with hyponatremia were identified. A total of 157 admissions without hyponatremia in October 2007 were used as controls. Variables were the use of SSRI, antipsychotic, antiepileptic (AED), and overall psychotropic medications. Age and gender were also analyzed.

Results: Mean age was 52.4 for cases and 43.0 for controls (p<0.0001), and 58.4% versus 63.1% were male (p=0.455), respectively. Antipsychotic use was significantly higher in cases. (51.5% versus 33.1%, p<0.005) This finding remained after adjusting for age by multiple logistic regression analysis. (odds ratio, 95%CI 1.1509-3.3185) There were no statistical differences in the use of SSRI (17.8% for cases and 12.7% for controls, p=0.261) or AED. (24.8% for cases and 20.4% for controls, p=0.409)

Conclusions: Among all the classes of psychotropic medication, antipsychotic use was the only statistically significant predictor of hyponatremia, even after adjusting for age. Unlike previous reports, SSRI and AED use were not significantly related to hyponatremia. We now need to bear in mind the effect of antipsychotics on developing hyponatremia. Age was a clear risk factor but gender was not in this study.

512. Association between DNA Methylation Patterns and Total Life Stress in Inner City Primary Care Patients

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Background: The role of repetitive psychosocial stress on the immune system has been well documented. Increasing evidence supports an association between inflammation and stress-related HPA axis dysregulation. In recent years, studies have highlighted the role of DNA methylation as a potential mediator of the long-term changes that result from chronic exposure to stress.

Methods: This study evaluated a group of African American subjects from general medical clinic waiting rooms in an urban public hospital. Total Life Stress (TLS) was assessed using the Stressful Events Questionnaire. We measured plasma levels pro-inflammatory cytokines (IL6, IL2 and TNF) using a multiplex ELISA in 177 subjects and extracted DNA from whole blood. We evaluated the association between TLS and all 27,578 CpG sites on the Illumina HumanMethylation27 BeadChip in 110 subjects using a linear regression, accounting for chip effects using random effects model.

Results: We observed increased IL6 (t=2.36; p=0.019), IL2 (t=2.08; p=0.039) and TNF (t=2.89; p=0.0044) concentrations with increased of TLS scores. Additionally, 5089 CpG loci were nominally associated with TLS (1.16E-7<p<0.05). Many CpGs were near interleukins and chemokines, but CpGs that met criteria for experiment-wide significance (p<1.81E-6) were in scores. Additionally, 5089 CpG loci were nominally associated with TLS (1.16E-7<p<0.05). Many CpGs were near interleukins and chemokines, but CpGs that met criteria for experiment-wide significance (p<1.81E-6) were in...
513. The Effect of Dopamine on Working Memory: Impact of Load, Dose and Genotype

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Background: Working memory (WM) performance may vary with dopamine availability along an inverted U-shaped curve and COMT polymorphism (val158-met) may underlie neural effects. To date, this model has not been fully tested using multiple amphetamine doses as probes of the dopaminergic system at smoothly parametric loads - factors influencing WM brain activity.

Methods: We predicted that in response to amphetamine, COMT val homozygotes (with less synaptic dopamine) would improve performance and cognitive efficiency (i.e., decreased BOLD change) during amphetamine while met/met would show stable/declining performance and increased/unchanged BOLD. Using placebo and 2 active amphetamine doses, we assessed 10 met/met and 8 val/val persons (mean age=29.2) with an fMRI verbal Sternberg paradigm that parametrically varied cognitive load. Data were analyzed using SPM5 factorial models (2 genotypes x 3 doses x 3 cognitive loads) separately for encoding, rehearsal, and recall.

Results: Behaviorally, val performed worse than met on placebo at low cognitive load (p<0.05), but improved (p<0.05) to met levels post-amphetamine. Our task engaged the dorso-ventrolateral prefrontal and parietal cortices as prior WM studies. As hypothesized, significant genotype x load, dose x load, and genotype x dose effects (p<0.05) consistent with the inverted-U model occurred throughout this WM network, but specifics varied somewhat by fMRI task phase.

Conclusions: Although these data support a genotype-specific optimal range for dopaminergic effects on WM, the peak of the range was not identified in our experiment and task context mattered to brain activity effects. COMT’s effects on dopaminergic function are not localized to the prefrontal cortex.

514. Fronto-Limbic Abnormalities in Adults with Attention-Deficit/Hyperactivity Disorder Comorbid with Bipolar Disorder using a Cortical Thickness MRI Analysis

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Background: Attention deficit-hyperactivity disorder (ADHD) and bipolar disorder (BPD) frequently co-occur and represent a particularly severe clinical form of both disorders. This comorbidity, however, has been poorly investigated by neuroimaging. Our goal was to evaluate the morphometric underpinnings of the comorbidity of ADHD with BPD in the cerebral cortex, using MRI cortical thickness analysis.

Methods: Morphometric MRI findings of cortical thickness were compared between 31 adults with ADHD+BPD and 23 controls. Furthermore, MRI cortical findings were compared between 26 adults with ADHD, without BPD, and 18 adults with BPD with the 23 controls.

Results: Compared to group matched controls, subjects with comorbid ADHD+BPD showed thinning in a cortico-limbic frontal lobe network including the lateral prefrontal, anterior cingulate and paracingulate cortices, as well as the medial frontal and orbitofrontal cortices, and the frontal pole. The profile of brain alterations in ADHD+BPD was different as compared to that of ADHD or BPD alone.

Conclusions: Results support the hypothesis that the comorbid condition of ADHD+BPD shows selective alterations in distinct brain structures subserving regulation of mood and cognition. Studying comorbidity is necessary to help clarify the heterogeneous neuroanatomy of both BPD and ADHD. Supported by NIMH-MH-62152

515. Methylphenidate- Mediated Reduction in Prefrontal Hemodynamic Responses to Working Memory Tasks: A Functional Near-Infrared Spectroscopy Study

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Background: Methylphenidate (MP) improves attention and working memory by enhancing the brain catecholamine function. However the neural mechanisms underlying its cognitive effects remain unclear. In this study we investigated the effect of MP on hemodynamic responses to resting condition and working memory tasks in bilateral prefrontal cortical brain regions using near infrared spectroscopy (NIRS).

Methods: Thirteen right handed healthy subjects underwent N-back working memory tasks with increasing difficulty (0-back, 2-back) before and after a single oral dose of MP 20 mg and placebo administered in a double blinded random order fashion on two separate days in a within-subject design. We measured changes in oxy-hemoglobin (Oxy-Hb) and deoxy-haemoglobin (Deoxy-Hb) concentration during the tasks and resting conditions before and after MP and placebo administration using 2-channel NIRS

Results: MP significantly decreased Oxy-Hb and total haemoglobin concentration in right lateral prefrontal regions during working memory tasks compared to resting state, whereas placebo did not show significant changes. Furthermore, baseline adjusted oxy-Hb in 2-back task (2-back minus resting) was significantly decreased in MP condition compared to placebo condition. There were significantly more correct responses and few omission errors during 2-back task performance with MP than with placebo. MP showed non-task related decreases in deoxy-Hb significantly in the left side.

Conclusions: This NIRS study results corroborated with previous PET findings that methylphenidate may reduce cognitive task-related lateral prefrontal activation probably by improving the task-specific neuronal signalling (efficiency of neural activity). The clinical utility of NIRS in the prediction of treatment responsiveness to psychostimulant medication needs further evaluation. Supported by Nil
516. Indices of the Metabolic Syndrome in Healthy Adults: Associations with Hypothalamic-Pituitary-Adrenal Axis Function

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Background: The metabolic syndrome is characterized by central obesity, and increases in blood pressure, insulin resistance, and hypercholesterolemia. Exposure to stress appears to play a role in the pathophysiology of the syndrome. More specifically, it has been suggested that excessive cortisol exposure may be responsible for such metabolic derangements, and recent studies have shown dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in individuals with features of the metabolic syndrome.

Methods: Healthy adults (113 men and 147 women) completed the dexamethasone/corticotropin-releasing hormone (Dex/CRH) test, and provided data for anthropometric measurements, heart rate, blood pressure, glycated hemoglobin (HgbA1c), total cholesterol, and HDL. In addition, participants reported on their history of early life stress as well as their physical health and well-being.

Results: Lower cortisol responses to the Dex/CRH test were associated with measures of central adiposity (p<.001), elevated diastolic blood pressure (<.05), and lower HDL cholesterol (<.05). Lower cortisol concentrations in the Dex/CRH test were also associated with measures of physical health and energy.

Conclusions: The results suggest that reduced HPA axis responsivity is associated with indices of the metabolic syndrome. The nature of the relationship of HPA axis responses with specific aspects of the metabolic syndrome as well as links to reports of childhood maltreatment and measures of physical health and energy will be discussed.

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517. Stress is Visible; Objective Assessment of Stress Based on Multiple Cytokines

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Background: Stress is major causative factor for psychiatric diseases, though there have been no biological means for objective assessment. Responses of hormones and monoamines after stress have been investigated, however, responses of cytokines and chemokines to stress have not.

Methods: 25-40 years old, 60 men and 60 women which were physically and psychologically healthy were loaded with Kraepelin’s test and Tread Mill for three hours. Blood were overtaken every hour, plasma levels of cytokines and chemokines were determined, and whether plasma cytokines levels reflect context and severity of stressor was examined by discriminant analysis.

Results: Participants loaded with Kraepelin Test or Tread Mill were serologically segregated with accuracy of 100%. Accuracy (mean of sensitivity and specificity) for seggregation between before and after load was elevated according to duration of loads and decreased by rest. 8 to 10 cytokines and chemokines selected, were enough to maximize the effect.

Conclusions: Kraepelin test and Tread Mill induces distinct levels of cytokines in plasma. It is revealed that responses of plasma cytokines and chemokines after stress do not follow the paradigm of classical stress response, a general adaptation syndrome, thus stress responses may be segregated and, further, categorized serologically basing on cytokines. Determination of host defense mediators in plasma may serve objective means for detection of high risk group for stress-related psychiatric disorders and indicators for stress coping.

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518. Dopamine Modulates the Default Mode Network in Parkinson’s Disease

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Background: The default mode network (DMN) is characterized by a deactivation of several cortical areas (including medial prefrontal cortex and posterior cingulate cortex) during goal-directed experimental tasks. Few findings are reported on DMN in Parkinson’s disease (PD) and the involvement of dopaminergic medication on this network.

To evaluate the effect of levodopa on brain deactivation, we conducted an fMRI study in non-demented, non-depressed PD patients compared to healthy volunteers.

Methods: Fourteen PD patients and thirteen healthy subjects received either levodopa or placebo in two fMRI sessions. Brain deactivation was evaluated during a facial emotion recognition task.

Results: While the control subjects showed a classical brain deactivation network during the emotional task, the PD patients taking placebo only deactivated the ventral medial prefrontal cortex. They failed to deactivate the posterior midline and lateral parts of the brain deactivation network compared to controls. After levodopa administration, this network was restored conjointly with the improvement of motor dysfunction in PD patients.

Conclusions: The levodopa effect on DMN is probably the consequence of a beneficial dopamine (DA) medication effect on the general (physical) state of the PD patients correcting the low level of DA in the basal ganglia. The absence of medial prefrontal deactivation impairment may suggest a preserved mesocortical DA system in these patients.

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519. Reliability of Performance and fMRI Bold Signal in the Cognitive Control Network during the Stroop Task

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Background: Functional MRI (fMRI) has become the prevailing noninvasive functional imaging modality for the study of the neural bases of cognitive processes, their impairments in neuropsychiatric disorders, and for assessing the effects of genetic variations and therapeutic interventions. However, the large variability in the fMRI blood oxygenation level dependent (BOLD) signal can pose a challenge when making comparisons across time.

Methods: We investigated the reliability of behavioral performance and BOLD activations in 15 healthy subjects performing a fast event-related version of the Stroop task in two sessions separate by 8 weeks. Intraclass correlation coefficient (ICC) analyses were conducted on regions-of-interest (ROIs) defined by standard regression techniques, and also at the whole-brain level.

Results: Behavioral analyses showed high ICCs for congruency effects. Significant activations were found in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) regions in both conflict- and error-related condition contrasts. For the ROI-based analyses, moderate magnitude ICCs were observed for the conflict- and error-related contrasts in the DLPFC and the ACC, respectively, while there were poorer ICCs for the other contrasts/regions despite their significant condition-related differences. Voxel-wise ICC analyses were consistent with these results.

Conclusions: These findings indicate that even higher cognitive and related neural processes such as those tapped in cognitive control paradigms such as the Stroop task can be indexed in a reliable manner. Thus, fMRI indices may serve as candidate biomarkers of pathophysiologic processes and the effects of novel therapeutics on cognitive control network disturbances in neuropsychiatric disorders.

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520. International Consensus Diagnostic Criteria for Neuroleptic Malignant Syndrome Using the Delphi Technique

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Background: Functional MRI (fMRI) has become the prevailing noninvasive functional imaging modality for the study of the neural bases of cognitive processes, their impairments in neuropsychiatric disorders, and for assessing the effects of genetic variations and therapeutic interventions. However, the large variability in the fMRI blood oxygenation level dependent (BOLD) signal can pose a challenge when making comparisons across time.

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Results: Behavioral analyses showed high ICCs for congruency effects. Significant activations were found in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) regions in both conflict- and error-related condition contrasts. For the ROI-based analyses, moderate magnitude ICCs were observed for the conflict- and error-related contrasts in the DLPFC and the ACC, respectively, while there were poorer ICCs for the other contrasts/regions despite their significant condition-related differences. Voxel-wise ICC analyses were consistent with these results.

Conclusions: These findings indicate that even higher cognitive and related neural processes such as those tapped in cognitive control paradigms such as the Stroop task can be indexed in a reliable manner. Thus, fMRI indices may serve as candidate biomarkers of pathophysiologic processes and the effects of novel therapeutics on cognitive control network disturbances in neuropsychiatric disorders.

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521. FDG-PET Regional Glucose Abnormalities in White Matter in Civilian Impact and Military Blast-Related Mild Traumatic Brain Injury

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Background: While numerous neuroimaging studies in civilian traumatic brain injury (TBI) have been published, no functional imaging studies have compared blast-related mild TBI, identified as the signature injury in veterans from Iraq and Afghanistan, to civilian TBI. Thus, questions remain whether blast-related TBI is a unique pathophysiologic entity or whether it is similar to civilian TBI, typically localized and related to vehicular impact.

Methods: [18F]FDG-PET images were obtained on seven combat veterans (2F, 5M; age=29.4±8.4 years) with blast-related mild TBI, 26 civilians (8F, 18M; age=38.4±8.2 years) with vehicular impact TBI, and 20 normal controls (9F, 11M; age=28.6±7.9 years). Subjects were administered 5mCi of intravenous [18F]FDG and they received a word list learning task during the 30-min uptake period. White matter structures were assessed with a stereotaxic region of interest atlas.

Results: Relative metabolic rate of the corpus callosum was increased anteriorly in the genu in blast and civilian TBI patients, whereas civilian TBI subjects subjects showed elevation in the body only; both groups had decrease in relative metabolic rate in the splenium (F=2.34, df =12,300, p=0.007), confirmed using MANCOVA with age as a covariate (F=2.08, Wilks .606, df=12,88, p=0.026). Blast-related TBI subjects showed increased metabolic rates in white matter in prefrontal areas and throughout the brain, whereas patients with civilian TBI showed less widely distributed increases, most prominently in the internal capsule and posterior corpus callosum.

Conclusions: Findings indicate an increase in white matter relative metabolic rate with traumatic brain injury, and a more widely dispersed pattern in blast-related mild TBI.
522. Subthalamic Nucleus Stimulation in Parkinson's Disease Induces Apathy: A PET Study
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Background: An increasing number of studies are reporting adverse effects of bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) in Parkinson's disease (PD), such as emotional disorders. In line with these reports, we recently found that apathy may be induced by STN DBS in PDI.

We had previously demonstrated a correlation between reduced recognition of facial emotions, especially fear, and changes in the glucose metabolism of PD patients undergoing bilateral STN DBS in the right orbitofrontal cortex. The objective of the present study was to correlate apathy induced by STN DBS with changes in glucose metabolism, using 18FDG-PET.

Methods: Twelve PD patients were assessed three months before (M-3) and three months after (M+3) STN DBS with 18FDG-PET and the Apathy Evaluation Scale.

Results: Apathy had significantly worsened at M3 after STN DBS. Positive correlations were observed between this variation in apathy scores and changes in glucose metabolism, especially in the right frontal middle gyrus (BA 10) and right inferior frontal gyrus (BA 46 and BA 47). Negative correlations between the two were observed in the right posterior cingulate gyrus (BA 31) and left medial frontal lobe (BA 9).

Conclusions: These preliminary results confirm the role of the STN in associative and limbic circuitry in humans and suggest that it is a key basal ganglia structure in motivation circuitry.

523. Transcranial Magnetic Stimulation for Fibromyalgia
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Background: Fibromyalgia (FM) is a generalized chronic pain syndrome of unknown etiology, but involves central sensitization. Depression is a common co-morbidity in FM. Repetitive transcranial magnetic stimulation (rTMS) modulates neural activity with antidepressant and anti-nociceptive effects.

We hypothesized there will be a reduction in pain, depression and improved quality of life with 10 day course of TMS.

Methods: In this 2-week, randomized, double blind trial, subjects with FM received rTMS or sham stimulation for 10 sessions left dorsal lateral prefrontal cortex (DLPFC). Active stimulation parameters were 10 Hz at 120% of motor threshold. Subjects receive 4000 pulses per session and 40,000 pulses total. Patient FM status was measured at baseline, at the end of each week of treatment (2 weeks), and 2 weeks after treatment by a continuous rater. Pain, depression, and quality of life indices were included. Hierarchical linear modeling was used for time series data including daily pain.

Results: Interim analyses suggest a 45% reduction in average daily pain in subjects receiving treatment by day 6 and 80% by day 10. This effect on average was maintained 10 days after the last treatment. There was a nonsignificant decrease in depression over the treatment course.

Conclusions: Interim results support rTMS may significantly reduce fibromyalgia pain before any antidepressant effects are observed. Future work may determine if rTMS may be an effective treatment for fibromyalgia given current limited treatment options. Supported by NIAMS, P60, MCRC.

524. Sensitivity of a Low-Cost Balance Platform for the Assessment of Postural Instability
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Background: Postural instability can be an important sign of neurological dysfunction in neuropsychiatric disorders such as traumatic brain injury (TBI), Parkinson’s disease, and multiple sclerosis. Studies have shown that a standard clinical exam may not be sensitive enough to detect subtle abnormalities. Commercial balance force platforms are effective but not used widely due to issues of cost and portability. Nintendo, a video game company, has developed an inexpensive and portable balance platform called the Wii Balance Board. No studies have yet looked at the reliability of these boards.

Methods: Custom software was written to allow a laptop to communicate with the board and record data. Two boards were tested, twice, with two levels of weight (34kg and 59kg). The large weight was centered and a 0.38kg weight was placed at each corner stepwise. The sensor values, mean, range, and standard deviation were calculated for each round. Ranges were averaged for each board and compared between boards.

Results: The data show the same board will produce values within a 15g range (stddev 5g). The average of the range between different boards will be within 5g. The total range variation is 20g between all boards. In a 70kg person, this is a maximum range of error of 0.11%.

Conclusions: The Wii Balance Board is a sensitive and inexpensive balance measurement device. With further development, it should be able to produce standard balance metrics comparable to commercial devices, allowing quantitative balance metrics to be easily collected in a wide range of populations. Supported by R01MH060662; P20DA024196

525. Phenomenology of Self in Delusions of Reference in Beginning Schizophrenia
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Background: Despite claims that neuroimaging experiments access human 1rst-person-perspective, studies to date examine self from a 3rd-person-perspective, e.g., retrospective reports, higher-order self-referential judgments, unconstrained default-mode activity putatively reflecting relaxed daydreaming or personal memories. Therefore, these approaches do not provide information.
Background: While dorsolateral prefrontal cortex (DLPFC) structural abnormalities may pre-date and predict psychosis onset, it is unclear how functional deficits manifest prior to onset. A computerized cognitive control measure (AXCPT) was used in two experiments including clinical-high-risk for psychosis (CHR), first-episode schizophrenia (SZ), early psychosis (EP), help-seeking psychiatric controls (PC), and healthy control (HC) participants. We hypothesized CHRs would show deficits on the AXCPT relative to HC with CHR performance intermediate between controls and patients (EP, SZ).

Methods: Study 1: CHR (n=103), EP (n=20), and PC (n=21) participants from six Early Detection Intervention for the Prevention of Psychosis Program (EDIPP) sites completed the AXCPT. Study 2: Demographically-matched CHR (n=20), SZ (n=30) and HC (n=30) individuals from the UC Davis Early Detection and Preventive Treatment (EDAPT) clinic performed the AXCPT during fMRI.

Results: Study 1: EPs demonstrated a specific deficit in cognitive control (AY-BX accuracy) compared to PCs. CHRs showed an intermediate deficit that did not differ from EP and PC participants. Study 2: When compared to HCs, CHRs demonstrated reduced cue-related DLPFC activation that was correlated with poorer performance and global functioning.

Conclusions: Individuals experiencing less than 30 days of psychosis show cognitive control deficits similar to those seen in SZ, demonstrating that cognitive impairment appears early in the development of psychotic illness. CHR individuals show cognitive control impairment and reduced DLPFC activation, compared to controls, that is associated with poor global functioning. Findings support early intervention strategies targeting cognition. Additional clinical and functional outcome data will be presented.

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527. Abnormal Face Processing in Schizotypal Personality Disorder

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Background: Recent studies indicate that social function in schizophrenia is impaired. Importantly, processing of faces in schizophrenia was found abnormal (e.g., Onitsuka, Niznikiewicz et al., 2006). In this study we examined if face processing difficulties observed in schizophrenia are also observed in Schizotypal Personality Disorder (SPD).

Methods: 14 right-handed SPD males and 14 normal comparison (NC) individuals matched for age, IQ, and parental SES saw 32 pictures in each category: neutral faces, cars, hands, and butterflies as their EEG was recorded. The pictures appeared in the center of the screen for 500 msec with 1900 inter-stimulus interval. Subjects responded to a target (butterfly). Individual averages were constructed to 3 non-target stimuli (100 msec pre-stimulus baseline and 900 post-stimulus epoch). N170 indexing processing face features was measured between 150-190 msec, post-stimulus. N170 amplitude and latency were analyzed

Results: N170 amplitude was more negative to faces (p< 0.028) relative to cars and hands, and there was a stimulus by group interaction (p<0.35). NCs showed larger N170 to faces relative to hands (p<0.002) and cars (p< 0.014) while similar N170 was observed in SPD to all stimuli. N170 to faces was reduced in SPD relative to NC (p< 0.04). N170 latency was shorter to faces (p< 0.0001) relative to hands and cars.

Conclusions: The lack of N170 amplitude differences as a function of stimulus and its reduction to faces in SPD suggest faces processing difficulties similar to those found in schizophrenia and indicate that social impairment in SPD is in part related to inefficient face processing.

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528. Clinical and Neurocognitive Similarities between the Bipolar and Schizophrenia Prodrome

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Background: There is an increased interest in early intervention strategies for severe mental disorders with hopes of mitigating the impact of the illness. Individuals at clinical high-risk for schizophrenia have been identified by...
the presence of attenuated positive symptoms and a significant decline in functioning. Although bipolar disorder and schizophrenia may have overlapping etiologies, few studies have investigated the potential prodrome in bipolar disorder. We sought to determine if there is a prodrome to bipolar disorder and if clinical or neurocognitive measures could distinguish between the bipolar and schizophrenia prodromes.

**Methods:** We examined subjects who were initially identified as clinical high-risk for schizophrenia during the prodromal phase of the illness and followed them prospectively. Unexpectedly, six subjects developed bipolar disorder. Thus, data from subjects who eventually developed bipolar disorder (BP; N=6), schizophrenia or a psychotic disorder (SZ; N=24) and healthy controls (HC; N=38) were compared.

**Results:** The BP and SZ groups did not differ on positive symptom severity, global measures of functioning, or on the overall neurocognitive score. Compared to the HC group, both patient groups reported more positive symptoms and impaired global functioning. The SZ group was significantly more impaired than the HC group on the overall neurocognitive score, whereas the BP group did not differ from the HC group.

**Conclusions:** This study supports the notion that there is a bipolar prodrome, which is indistinguishable from the schizophrenia prodrome based on clinical and neurocognitive measures. Supported by R21MH08024

529. Baseline Cognitive Performance in Psychiatric Patients and Healthy Volunteers Using a Computerized Neurocognitive Battery

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**Background:** Neurocognitive deficits are recognized as important treatment targets in psychiatric disorders. This analysis examined cognitive performance in healthy volunteers to guide the interpretation of cognitive data in psychiatric patients.

**Methods:** Data were obtained from studies of healthy volunteers and 2 patient populations: treatment-resistant depression (TRD) and schizophrenia (SCZ). The Cogtest® computerized neurocognitive test battery yielded information in various cognitive domains (processing speed [PS], attention/vigilance [A/V], reasoning/problem-solving [R/PS], working memory [WM], declarative memory [DM], and social cognition [SC]) and a total neurocognitive composite score (NCS). Baseline cognitive data were assessed.

**Results:** Data were available for 124 healthy volunteers, 366 subjects with TRD, and 323 subjects with SCZ. T-scores of 50.0 (SD=10) were created for healthy volunteers for the NCS and cognitive domain scores based on age and sex. In comparison, mean baseline NCSs were lower for SCZ (37.5) than for TRD subjects (46.7). TRD subjects' mean domain scores were slightly lower than for healthy volunteers (PS=46.2, A/V=47.9, R/PS=49.4, DM=49.8). As expected, SCZ subjects were more impaired: mean domain scores were comparable to healthy volunteers for SC (48.9) and R/PS (49.2) but were lower for PS (40.8), A/V (39.8), WM (30.4) and DM (40.6).

**Conclusions:** Normative data from a computerized cognitive test battery is consistent with earlier reports suggesting that SCZ patients have impaired cognitive functioning versus age- and sex-matched healthy volunteers. Subjects with TRD exhibited more subtle attention and memory deficits. Supported by Ortho-McNeil Janssen Scientific Affairs, LLC.

530. Recognition of a Facial Affect in a Situation Where Various Emotions Interact with Each Other in Patients with Schizophrenia

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**Background:** Recognition of a target emotion displayed by others becomes more complex when various emotions coexist. Emotion recognition task in previous studies included only target emotion, which might not reflect the probable complex emotional interaction. To measure emotional deficits in a situation where emotions interact, we constructed a novel task during which a target (small face) was presented on a distracting background (large face).

**Methods:** 22 patients and 21 controls participated. The task included three conditions according to background facial emotion: happy background, fear background, and baseline conditions. In happy and fear background conditions, target faces were presented on happy and fear background faces, respectively. In baseline condition, blank was substituted for the background face. Target stimuli included neutral, happy, and fear faces. Subjects were required to identify target emotions.

**Results:** The performance of patients vs. controls become worse in the presence of distracting background emotion (F(2,39)=7.98, p < .01). Emotional deficit of patients with schizophrenia was more pronounced in recognizing fear vs. happy and neutral (F(2,39)=3.27, p < .05). Significant interaction of background-by-target emotion (F(4,37)=3.31, p < .05) showed that the interference is dependent on the combination of background and target emotions.

**Conclusions:** The present study demonstrate that recognition of target emotion is influenced by background emotion. To our knowledge, this is the first which showed interactions between emotions. These findings suggest that patients experience more errors recognizing target emotion when emotions coexist and that it is necessary to employ the background condition to explore emotional deficits of schizophrenia.

531. ERN Across the Illness Course of Schizophrenia

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**Background:** The error-related negativity (ERN) component of the event-related potential (ERP) reflects neural activity associated with execution of an error; correct-response negativity (CRN) is associated with correct responses. Patients with chronic schizophrenia have ERN reductions and CRN enlargements, reflecting deficits in response monitoring. We asked if this pattern develops during the course of the illness, from prodromal to chronic stages of the illness.
Methods: We recorded ERPs to error and correct responses during a picture-word matching task from chronic schizophrenia patients (SZ; n=9), first-episode schizophrenia patients (FE; n=23), prodrome subjects (PD; n=18), and their age-matched healthy controls (HC; n=10, n=27, n=21, respectively).

Results: ERN activity was significantly diminished in SZ and FE (p<0.01 and p<0.008, respectively), and marginally diminished in PD (p<0.08). CRN values were marginally enlarged in SZ (p=0.08) and significantly enlarged in FE (p<0.038), but did not show a significant enlargement in PD. Performance accuracy matched neural activation. SZ and FE showed significantly higher error percentages than HC; PD did not.

Conclusions: Evidence supports the developmental trajectory of schizophrenia and illustrates the relationship between cognitive control and severity of illness over the course of schizophrenia. These data are indicative of heterogeneity within the prodrome, and suggest that subgroups of potential nonconverters to psychosis may dilute the strength of the cognition-severity of illness relationship.

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531. Memory Processing among First Degree Relatives of Schizophrenia Subjects

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Background: Episodic memory deficits are proposed as potential intermediate phenotypes. We attempt to characterize deficits in encoding/retrieval among schizophrenia (SZ, n=19), first degree relatives (HR, n=15) and controls without personal or family history of psychotic disorders (HS, n=25).

Methods: Subjects were administered Structured Clinical Interview for DSM IV (SCID) to confirm the presence or absence of schizophrenia/schizoaffective disorder. All subjects underwent functional imaging on 3T Siemens Trio scanner while performing episodic memory encoding and retrieval task. Whole-brain BOLD response differences were analyzed using SPM5 correcting for multiple comparisons using false discovery rate (FDR) approach and were correlated with in-scanner performance (response time and accuracy).

Results: There was an incremental increase in response time among the study groups (HS<HR>SZ) with no differences in accuracy in both encoding and retrieval. We observed an incremental increase in BOLD response to retrieval; increased BOLD response was observed at Brodmann area, BA9 (HR<HS); BA8/9 (SZ<HR) and BA19/46 (SZ<HS). In addition, SZ showed increased activation in the inferior and middle frontal gyrus (BA46/47), cingulate cortex (BA24/32), putamen, globus pallidus and amygdala compared to HS, and anterior cingulate cortex (BA24) and thalamus compared to HR. HR showed increased activation in the putamen and superior temporal gyrus compared to HS. We did not observe differences in BOLD responses while encoding.

Conclusions: Elevated familial risk for SZ may be associated more effortful processing of episodic memory retrieval. Lack of BOLD response differences may be secondary to relatively deeper processing required to perform the task.

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532. Brain Activation Patterns during Episodic Memory Processing among First Degree Relatives of Schizophrenia Subjects

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Background: Episodic memory deficits are proposed as potential intermediate phenotypes. We attempt to characterize deficits in encoding/retrieval among schizophrenia (SZ, n=19), first degree relatives (HR, n=15) and controls without personal or family history of psychotic disorders (HS, n=25).

Methods: Subjects were administered Structured Clinical Interview for DSM IV (SCID) to confirm the presence or absence of schizophrenia/schizoaffective disorder. All subjects underwent functional imaging on 3T Siemens Trio scanner while performing episodic memory encoding and retrieval task. Whole-brain BOLD response differences were analyzed using SPM5 correcting for multiple comparisons using false discovery rate (FDR) approach and were correlated with in-scanner performance (response time and accuracy).

Results: There was an incremental increase in response time among the study groups (HS<HR>SZ) with no differences in accuracy in both encoding and retrieval. We observed an incremental increase in BOLD response to retrieval; increased BOLD response was observed at Brodmann area, BA9 (HR<HS); BA8/9 (SZ<HR) and BA19/46 (SZ<HS). In addition, SZ showed increased activation in the inferior and middle frontal gyrus (BA46/47), cingulate cortex (BA24/32), putamen, globus pallidus and amygdala compared to HS, and anterior cingulate cortex (BA24) and thalamus compared to HR. HR showed increased activation in the putamen and superior temporal gyrus compared to HS. We did not observe differences in BOLD responses while encoding.

Conclusions: Elevated familial risk for SZ may be associated more effortful processing of episodic memory retrieval. Lack of BOLD response differences may be secondary to relatively deeper processing required to perform the task.

Supported by MH72995

533. Adolescent Offspring of Schizophrenia Patients Show Reduced Amygdala-Related Modulation of Memory Systems During Affective Memory Task

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Background: Studies indicate that the amygdala modulates activity in the memory systems of the healthy brain (Packard & Teather, 1998). This modulation may reflect normal functioning of the fronto-limbic affective pathway. Adolescent offspring of schizophrenia patients (Scz-Off) are an important group in whom to study impaired processing within this pathway. We assessed amygdala modulation of frontal and striatal regions to negatively valenced stimuli during an affective appraisal task in a group of Scz-Off and control subjects (HC) with no family history of psychosis.

Methods: Nineteen Scz-Off (7 females, mean age = 14.3 yrs) and 25 HC (8 females, mean age = 14.6 yrs) participated. fMRI, faces (Ekman & Oster, 1979) and control images were presented (3s/faces) sequentially. Subjects judged if the affect depicted on a face was the same as that on the previous face. fMRI was conducted on a Bruker MedSpec 4T system (345 EPI scans; TR=2s; 24 slices; 3.8x3.8x3mm). Modulatory interactions were assessed using Psychophysiological Interaction (PPI; Friston et al., 1997), with amygdala as the seed.

Results: Scz-Off showed significantly reduced amygdala modulation of prefrontal cortex (t83=-2.78, qFDR<.05, x=-22, y=41, z=37) and a trend toward reduced amygdala modulation of basal ganglia (t83=-2.08, qFDR<.1, x=-18, y=-2, z=5) than HC in response to negative stimuli.

Conclusions: Reduced amygdala modulation of memorial regions may reflect a disordering in the critical fronto-limbic affective pathway in Scz-Off, and may underlie deficits in social behavior during adolescence that are characteristic of this population.

Supported by NIMH68680

534. Effect of Rule Maintenance on Episodic Memory in Schizophrenia

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Background: Individuals with schizophrenia have difficulty maintaining rules to guide behavior, leading to errors on inhibition tasks like the Stroop. The current study tests whether these same rule maintenance problems may also explain patient difficulties with control of episodic encoding and retrieval.

Methods: Twelve healthy controls and thirteen patients underwent fMRI while encoding words during 2 conditions: 1) "Rule" - a living/nonliving judgment was made when the color of target words matched the color of a surrounding box. A "skip" response was made when color of non-target words did not match. 2) "No-Rule" - living/nonliving judgments were made for all words. Subjects were instructed to encode only items for which they made a living/non-living judgment. A subsequent recognition task was performed outside the scanner requiring discrimination of target and non-target items from new items.

Results: There were no group differences in encoding task performance, with both groups performing above 90%. Subsequent memory analysis did not reveal any group differences in the No-Rule condition. There was a group difference
535. The Deluded Brain

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Background: Examining the neural correlates of delusions is more difficult that discrete psychotic phenomenon like hallucinations. In general structural MRI and PET studies have implicated temporal-limbic and frontal regions. However, there have been few studies to examine neural correlates of cognitive models of delusions. This study examined whether the semantic memory model of delusions.

Methods: Fifteen chronic schizophrenia patients, with diverse symptom profiles, and 15 healthy volunteers performed a semantic priming task during event-related fMRI. During the task, participants responded to target words shortly preceded by either related or unrelated “prime” words. Correlational analyses were conducted in the schizophrenia patients between responses to related, relative to unrelated, word pairs and different psychotic symptoms.

Results: Abnormal responses to related, relative to unrelated, word pairs were identified in schizophrenia patients with delusions in the left superior frontal gyrus (SFG). Controls exhibited greater responses to related relative to unrelated word pairs in the SFG, as did patients without delusions; however, patients with delusions showed greater responses to unrelated word pairs. No significant relationships were identified with hallucinations or thought-disorder.

Conclusions: Our results support the hypothesis that delusions in schizophrenia are related to left prefrontal dysfunction and disturbances in semantic memory processing.

Supported by NARSAD young investigator

536. A D-Amino Acid Oxidase Diplotype is Associated with Deficient PPI and Attenuated Anxiety in Healthy Males

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Background: Prepulse inhibition (PPI) of the startle reflex has been proposed as an endophenotype for schizophrenia. There is evidence supporting a role for the DAO locus in this disorder. The impact of DAO polymorphisms on PPI, neurocognitive performance and personality traits is still unknown.

Methods: We selected the D-amino acid oxidase (DAO) polymorphisms included in the SzGene database (rs4623951, rs2111902, rs3918346, rs3741775, rs3825251). These polymorphisms were analyzed in 530 healthy males, phenotyped for acoustic startle and prepulse inhibition, neurocognitive tasks and personality dimensions from the Eysenck Personality (EFPQ), Tridimensional Personality (TPQ), State-Trait Anxiety (STA), Schizotypy (STQ) and Behavioral Approach/Inhibition System (BIS/BAS) questionnaires. QTIPHASE from the UNPHASED package was used for the association analysis of allelic data, with p values corrected for multiple testing by running 10000 permutations of the data.

Results: The rs4623951_T and rs3741775_G diplotype was associated with deficient PPI (p<0.002). Moreover, subjects homozygous for the rs4623951_T and rs3741775_G alleles made more errors on a working memory task (p<0.006), and had lower STA (p<0.018), EPQ neuroticism (p<0.004), TPQ harm avoidance (p<0.042) and higher EPQ extraversion (p<0.002).

Conclusions: Healthy human subjects carrying the rs4623951_T and rs3741775_G diplotype have deficient PPI and working memory and attenuated anxiety. The rs4623951_T allele is the DAO polymorphism most strongly associated with schizophrenia and this allele might tag a haplotype that affects PPI, cognition and personality traits in general population.

537. Adolescent Schizophrenia Offspring with Prodromal Symptoms Show Hypoactivation in Fronto-Striatal Regions During Sustained Attention Task

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Background: Adolescent offspring of schizophrenia patients (SCZ-Off) are characterized by an increase in prodromal symptoms (Diwadkar & Keshavan, 2004). However, the relationship between observed symptoms and independent measures of brain function in this group are not understood. In a group of SCZ-Off, we evaluated whether prodromal symptoms modulated activity in fronto-striatal regions during sustained attention.

Methods: Nineteen controls (HC; no family history of psychosis to the 2nd degree; age=14.4 yrs) and 14 SCZ-Off participated. SCZ-Off were cleaved into high and low functioning sub-groups based on the GAF-M (Miller et al., 2003); SCZ-Off-HF were characterized by absent or minimal prodromal symptoms (n=5; 3 males; mean age=13.2), SCZ-Off-LF were characterized by transient to severe prodromal symptoms (n=9; 7 males; mean age=13.4). During fMRI (4T Bruker MedSpec) all subjects performed a modified continuous performance task (identical pairs). Three digit numbers were presented in rapid sequence (50ms, 250 ms SOA); subjects indicated when a number was repeated. Control epochs used passive viewing. Data were processed with SPM5.

Results: Relative to both HC and SCZ-Off-HF, SCZ-Off-LF showed significant hypo-activation in fronto-striatal regions central to sustained attention including the anterior cingulate, dorsal-lateral prefrontal cortex and basal ganglia (Maldjian et al., 2003; t28=3.71, pFWE<.05, x=-6, y=9, z=-25; t28=4.50, pFWE<.05, x=-30, y=19, z=-32; t28=3.01, pFWE<.05, x=14, y=8, z=11). By comparison, no differences were observed in primary visual cortex.

Conclusions: Objective measures of cortico-striatal function during fundamental processing may be sensitive to prodroem related clinical symptoms in SCZ-Off. The clinical relevance of these findings remains to be explored.

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538. Dissociating Inhibitory Control Deficits in Schizophrenia

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Background: Deficits of cognitive control have been repeatedly reported in Schizophrenia. Contrary to the view of a single cause underlying these effects (either a generalized deficit associated with task difficulty, or a specific deficit leading to widespread consequences), we hypothesized that specific control processes, operating at different stages of processing, may be impaired.

Methods: We tested 18 Schizophrenics and 21 matched-controls on item-recognition tasks that measured the abilities to ignore distracting perceptual information and suppress intruding information in working-memory. In the “Ignore” task, subjects saw a cue to remember either red or blue words, followed by a word-set (2 red, 2 blue), and a memory probe. The “Suppress” task was identical, except the word-set came before the instruction-cue.

Reaction time and percent error for dropped-negatives (probes subjects had to drop from working-memory) and non-familiar-negatives (probes that hadn’t appeared in the word-set) were obtained. Inhibitory control was calculated as the difference between dropped- and non-familiar-negatives.

Results: Compared to controls, on reaction time, Schizophrenics were impaired in the Suppress task, but not the Ignore task. Further, the magnitude of this deficit was correlated with disorganization symptoms.

Conclusions: These results are among the first to show a clear dissociation between inhibitory deficits in Schizophrenia. Importantly, these findings contrast with those obtained with Depressed and Obsessive-Compulsive disorder patients, who show no deficit in either Suppress or Ignore with comparable materials.

Table 1:

<table>
<thead>
<tr>
<th>Task (Ignore/Suppress) x Probe (ON/OF) x Group (SCI/Control)</th>
<th>Reaction Time</th>
<th>Percent Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task</td>
<td>F (1,37) = 41.87, p &lt; .000</td>
<td>F (1,37) = 17.19, p &lt; .000</td>
</tr>
<tr>
<td>Probe</td>
<td>F (1,37) = 75.02, p &lt; .000</td>
<td>F (1,37) = 23.57, p &lt; .000</td>
</tr>
<tr>
<td>Group</td>
<td>F (1,37) = 15.26, p &lt; .000</td>
<td>F (1,37) = 2.84, p = .10</td>
</tr>
<tr>
<td>Task X Probe</td>
<td>F (1,37) = 75.24, p &lt; .000</td>
<td>F (1,37) = 17.12, p &lt; .000</td>
</tr>
<tr>
<td>Task X Probe x Group</td>
<td>F (1,37) = 7.23, p = .01</td>
<td>F (1,37) = .28, ns</td>
</tr>
</tbody>
</table>

Summary Statistics

<table>
<thead>
<tr>
<th>Reaction Time</th>
<th>Percent Error</th>
</tr>
</thead>
<tbody>
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<tr>
<td>Task X Probe x Group</td>
<td>F (1,37) = 7.23, p = .01</td>
</tr>
</tbody>
</table>

539. Auditory Stream Segregation in Schizophrenia

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Background: Deficits in auditory processing have been clearly documented in individuals with schizophrenia (SZ), and are associated with reduced cortical gray matter in auditory cortices. However, it is not known whether this causes problems in perceptual organization of sound patterns. Therefore, the purpose of this study is to determine whether auditory stream segregation is impaired in SZ patients.

Methods: Low tones (A) and high tones (B) were presented to SZ patients and control participants in repeating ABA patterns for 6.72 sec, with a frequency separation of 3, 6, or 12 semitones (40 trials per frequency separation). At the end of each trial, participants indicated whether they heard one stream of sounds (ABA-ABA-) or two streams of sounds (A-A-A-A- and -B--B--).

Results: SZ patients were less likely than controls to report hearing two streams (main effect of group, p < .001). For both groups, larger frequency separation resulted in more perception of two streams (main effect of frequency separation, p < .001), a well-replicated effect in healthy individuals. However, the effect of frequency separation was smaller in SZ patients than controls (group x frequency separation interaction, p < .001).

Conclusions: The reduced effect of frequency separation on perception of two streams in SZ patients suggests sensory-level impairments, rather than a difference in decision criterion. Sensory-level impairments may arise from abnormalities in brain areas critical for the organization of sound on the basis of sound frequency in SZ patients, which could contribute to known difficulties in language processing and social interaction.

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Background: Prior research indicates that schizophrenia patients (SZs) are impaired at identifying themselves as the source of self-generated information (reality monitoring). In healthy controls (HCs) proper reality-monitoring is associated with increased activation in the medial prefrontal cortex (mPFC), but is absent in SZs (Vinogradov et al. 2008). Here, we investigated whether this deficit is amenable to a behavioral intervention.

Methods: Thirty-one SZs and 15 HCs underwent an fMRI source-memory task at baseline. Fourteen SZs were then randomly assigned to 80 hours of computerized targeted-cognitive-training (TCT) that focused on training auditory, visual and social cognitive processes. The other 14 SZs were assigned to a control condition of 80 hours of computer-games (CGs). All subjects repeated the task after 16weeks.

During scanning, subjects were asked to remember whether or not they had generated a target word on an earlier sentence-completion task. BOLD fMRI activity was measured on a 3T GE scanner before and after the 16-week intervention. Images were analyzed using SPM2.

Results: At baseline, SZs revealed significantly more impairments, compared to HCs, while recalling self-generated information (p=.0005) (Figure1). SZs also did not show mPFC activation that the HCs revealed when recalling self-generated versus externally-derived information (i.e., a self-referential effect). However, after 16weeks of targeted-cognitive-training compared to baseline, SZs showed increased activation in the same mPFC region that HCs revealed during self-referential processing (Figure 2).

Conclusions: These fMRI results indicate a possible “restorative” effect of targeted-cognitive-training in schizophrenia patients, whereby behavioral performance on a source-memory task is improved and brain activation patterns are “normalized.”
541. Sensitization, Epileptic-Like Symptoms and Local Synchronization in Patients with Paranoid Schizophrenia

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Background: Recent findings indicate that changes in synchronization of neural activities underlying sensitization and kindling could be more comprehensively understood using nonlinear methods.

Methods: With this aim we have examined local synchronization using novel measure of coarse-grained information rate (CIR) in 8 EEG signals recorded at different cortical areas in 44 patients with paranoid schizophrenia.

Results: The values of local synchronization that could reflect sensitization related changes in EEG activities of cortical sites were then related to psychometric measures of epileptic-like symptoms and positive and negative schizophrenia symptoms (PANSS). While no significant correlations between CIR and positive and negative symptoms have been found, statistically significant relationships described by Spearman correlation coefficients between CIR indices and results of LSCL-33 have been observed in 7 (of 8) EEG channels (r in the range from 0.307 to 0.374, p<0.05).

Conclusions: Results of this study provide first supportive evidence for the relationship between local synchronization measured by CIR and epileptic-like symptoms in schizophrenia.

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542. Theta Synchronization Abnormalities in Schizophrenia on a Lexical Decision Task

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Background: Synchronous activity of local and distributed neural circuits has been postulated as the physiological underpinning for distributed cognitive processing. Retrieval of an object from memory requires activation of a spatially distributed semantic network. Language studies have shown the importance of synchronization in the theta frequency range (4 - 8 Hz) in this semantic retrieval. The current study utilized a lexical decision task (words vs non-words) in psychiatrically-well participants and individuals with schizophrenia and examined language-related neural synchronization in the theta range.

Methods: 39 controls and 17 individuals with schizophrenia performed a lexical decision task, comprising 100 word-word pairs and 100 word-nonword pairs. Wavelet analysis between 2-20 Hz was utilized to derive evoked power, total power and intertrial phase locking (PLF). Theta was measured as the mean activity over the 200-400 ms post stimulus interval in the 3.7-4.8 Hz range.

Results: Controls showed a greater PLF (p < .001) and evoked power (p< .001) than patients. PLF was greater to word than non-words in both controls and individuals with schizophrenia (p = .03).

Conclusions: Both patients and controls showed increased trial to trial phase synchronization to words than to non-words, suggesting the task was sensitive to access of semantic stores. However, individuals with schizophrenia showed deficits in overall PLF and evoked power measures of neural synchronization in theta, which likely index efficiency of semantic network activation.

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Background: White matter (WM) abnormalities have consistently been reported in several brain regions of schizophrenic patients. It is unclear whether these abnormalities affect single WM structures or entire connective networks. We utilized an automatic fiber clustering method to separate anatomically distinct fiber tracts and estimate connectivity between brain regions. Factorial analyses on WM integrity and neuropsychological measures were conducted to better characterize anatomy of the functional networks implicated in schizophrenia.

Methods: 26 chronic schizophrenics and 24 matched healthy controls underwent Diffusion-Weighted scanning on a 3T magnet and a neuropsychological battery. After whole-brain tractography, two-hundred fiber clusters were automatically extracted from each subject based on fiber shape and location. These clusters were manually sorted into anatomically meaningful fiber bundles; mean Fractional Anisotropy (FA) was extracted from all bundles for all participants, compared between groups, and subjected to factorial analysis.

Results: Group comparisons demonstrated significant reductions in FA in the inferior longitudinal fasciculus and Genu of the corpus callosum (p=0.039 and p=0.046, respectively) in schizophrenia. Independent Component Analysis grouped fiber bundles into factors which were associated with memory, executive functioning, learning, and intelligence measures. This relationship between network anatomy and function remained strong in schizophrenics, suggesting that entire networks related to functional deficits of schizophrenia, rather than single fiber bundles, are affected.
Conclusions: Results suggest that WM fasciculi can be grouped into functional networks based on FA values, and the integrity of these networks are associated with neuropsychological functioning. Furthermore, abnormalities in those networks are associated with the cognitive deficits of schizophrenia.

Supported by NIH K05 MH070047 (MES); R01 MH 50740 (MES); R01 MH 40799 (RWM); R01 MH 074794 (CFW); P50 MH 080272 (RWM, MES); VA Merit Award (MES,RWM); VA Schizophrenia Center Grant, (RWM/MES); NIH U54 EB005149 (MK, RK, MES)

544. Parametric Variation in Working Memory Demand in Patients With Schizophrenia: A Behavioral and Neuroimaging Pilot Study

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Background: Patients with schizophrenia exhibit clinically relevant deficits in working memory (WM). However, investigations of WM using functional Magnetic Resonance Imaging (fMRI) have failed to reveal a consistent abnormality in brain activation in patients. One hypothesis is that patients exhibit a disordered relationship between the extent of activation in dorsolateral prefrontal cortex (DLPFC) and WM demand. Evaluating this hypothesis requires a task that permits fine-grained variations in WM demand.

Methods: Ten patients with schizophrenia and 9 matched control participants completed a behavioral version of the self-ordering task, and 11 unmatched control participants completed the task during an fMRI scan. On each trial participants were presented with an array of 8 complex 3D objects in 8 steps. On each step participants select any object they have not previously selected, and the objects’ spatial positions are re-randomized.

Results: Patients and controls exhibited above chance accuracy from steps 3 through 8, with patients performing significantly worse than controls at each of these steps. Least-squares fitting of a simple capacity model of task performance provided capacity estimates of 1.9 and 4.2 items for patients and controls, respectively. fMRI data indicated that controls exhibit an inverted-U relationship between step number and fMRI bold response in DLPFC and posterior parietal regions.

Conclusions: The self-ordering task is a valid means of assessing the effects of WM demand on brain activation, and elicits deficits in performance and WM capacity in patients relative to control participants. This makes it a promising technique for elucidating the nature of WM deficits in patients with schizophrenia.

545. Investigation of Endophenotype Candidates for Schizophrenia: A Study of Magnocellular Pathway in Refractory Patients and their Relatives

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Background: Schizophrenia is associated with deficits in higher-order processing of visual information. Such deficits may contribute for some symptoms as lack of attention, disturbances of visual memory and executive functioning. Previous research suggested that genetic loading for schizophrenia is related to a dysfunctional magnocellular (M) subcortical visual pathway. The purpose of this study was to evaluate the magnocellular pathway deficits in refractory schizophrenia using the frequency doubling technology (FDT-MATRIX) comparing with their relatives.

Methods: A total of 13 patients and 13 relatives and 19 controls were prospectively enrolled. After a complete ophthalmological examination, those with any ocular disease or previous oculars surgery were excluded. Patients were excluded if they had uncontrolled neurological disorder that might affect their performance. All patients and their parents underwent to FDT-MATRIX perimetry after a careful explanation. The test was performed in one session. The MD (mean-deviation) for each eye was used for analysis. Generalized estimated equation was performed to evaluate differences among the groups and to correct the dependency between the eyes.

Results: The mean MD (presented as the mean of both eyes but, for calculation, each eye was considered separately) was significantly lower for schizophrenia group (-4.35 dB ± 0.85) in comparison with their parents (-0.23dB ± 0.63) and for the control group (0.74 dB ± 0.33) (p<0.01). There was no significant difference between control group and schizophrenic parents group (p=0.244).

Conclusions: There is a lower mean MD with FDT MATRIX for schizophrenia parents comparing with control group but the difference did not reached statistical significance. Schizophrenic patients presented a significant lower MD. These findings suggest that the magnocellular pathway deficits could be considered as main aspects for future research on endophenotypes. Supported by Unfended

546. WITHDRAWN

547. Task-Positive and Task-Negative Neural Networks Involved in Working Memory Show Decreased Neural Efficiency at a High Working Memory Loads in Schizophrenia

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Background: Functional magnetic resonance imaging (fMRI) studies of working memory have suggested that this impairment is attributable to reduced information processing efficiency. In the current study we consider this theory with respect to a connected network of regions under different working memory load conditions.

Methods: We used constrained principal component analysis (CPCA) with a finite impulse response (FIR) basis set to compare the estimated hemodynamic response function associated with different levels of working memory load using the Sternberg Item Recognition Test (SIRT) on 15 healthy control subjects and 13 schizophrenia patients.

Results: Two reciprocally related components emerged, reflecting activated (task-positive) and deactivated (task-negative) neural networks. The estimated BOLD response was highly similar for patients and controls in the low load conditions, but in the 6-letter condition, the estimated BOLD signal peaks were more extreme for the patient group, and in the 8-letter condition, the estimated BOLD signal peaks were more extreme for the control group. Partialing the variance attributable to these networks out of the BOLD signal and re-running the analysis on the two groups separately suggested that there were no neural networks employed by one group and not the other.

Conclusions: (1) when task demands become sufficiently high, the task-positive and task-negative neural networks will reduce activation and suppression, respectively, and (2) patients experience a higher intrinsic working memory load than controls for overtly equivalent experimental conditions, supporting...
the theory that patients possess a reduction in efficiency of neural firing.

Supported by MSFHR, CIHR, NSERC

548. Intact Associative Learning in Schizophrenia: Evidence from a Go/NoGo Paradigm

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Background: Schizophrenia is associated with deficits in executive control and associative learning. One aspect of executive control, response inhibition, has traditionally been studied using Go/NoGo paradigms. In this study, we used a recently developed Go/NoGo paradigm to investigate associative learning in healthy control subjects and patients with schizophrenia.

Methods: Thirty patients with schizophrenia and 30 age-and-gender matched healthy control subjects performed 15 blocks of training and 3 blocks of test trials. The trials consisted of responding to words denoting either living or non-living objects. During training, subjects were instructed to respond by pressing the space bar (Go-task) to one of the word types (living or non-living objects), but not the other. During the test, the Go/NoGo mapping was reversed. Subjects were instructed to respond as quickly and as accurately as possible. Reaction times (RT) and accuracy were recorded for each trial and all subjects were debriefed upon completion of the test trials.

Results: Patients with schizophrenia had significantly longer Go RTs when compared to the control group, during both training and test trials. However, the two groups did not differ on any measure of associative learning.

Conclusions: Our findings suggest that associative learning is intact in schizophrenia patients during the performance of a relational Go/NoGo paradigm.

Supported by RO1MH073879; RO1MH070560

549. γ–Aminobutyric Acid Concentration is Reduced in Visual Cortex in Schizophrenia and Correlates with Orientation-Specific Surround Suppression

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Background: The gamma-aminobutyric acid (GABA) hypothesis proposes that reduced GABA concentration and neurotransmission in the brain results in cognitive impairments in schizophrenia. However, few in vivo studies have directly examined this hypothesis in individuals with schizophrenia.

Methods: We employed magnetic resonance spectroscopy (MRS) to measure visual cortical GABA levels in subjects with schizophrenia and demographically matched healthy control subjects. We further tested the GABA hypothesis by examining the relationship between GABA levels and orientation-specific surround suppression, a behavioral measure of visual inhibition thought to be dependent on GABAergic synaptic transmission.

Results: We found that the schizophrenia group had ~10% reduction in GABA concentration relative to the control group. For subjects with both MRS and behavioral data, we found a highly significant positive correlation between visual cortical GABA levels and magnitude of orientation-specific surround suppression. ANCOVA demonstrated that this relationship remained significant after accounting for group differences in GABA levels. Concentrations of GABA in visual cortex were not correlated with overall contrast discrimination performance for stimuli that did not contain a surround.

Conclusions: These results suggest that a deficit in neocortical GABA in the brains of subjects with schizophrenia results in impaired cortical inhibition and that GABAergic synaptic transmission in visual cortex plays a critical role in orientation-specific surround suppression.

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550. Prolactin, Smoking Status and Cardiovascular Risk in Community Psychiatric Patients

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Background: Previous studies in the general population have reported conflicting evidence regarding the relationship between prolactin levels, smoking status and cardiovascular risk. We investigated the prevalence of hyperprolactinaemia and tested the hypothesis that increased prolactin levels are associated with increased cardiovascular risk.

Methods: Prolactin levels and cardiovascular risk factors (smoking status, anthropometric measures and fasting plasma glucose and lipid levels) were assessed in 403 community psychiatric patients from across the diagnostic spectrum, in a cross-sectional naturalistic setting in the North East of England, UK.

Results: Mean age was 46.6 (±12.2) years and 50% (n=203) of the population was male. Hyperprolactinaemia was present in 19% of the sample, and in 24.6% of those prescribed antipsychotics. Hyperprolactinaemia was more prevalent in females (23%) compared with males (15%, χ²=3.9, d.f.=1, p=0.05). There was a statistical trend towards a negative correlation between prolactin and amisulpiride dose (p=0.06), but no relationship with dose for other antipsychotics. Serum prolactin levels (445.2±493.7mIU/l vs 834.2±1367.2mIU/l, p=0.001) and the prevalence of hyperprolactinaemia (34.7% vs 54.1%, p=0.004) were lower in cigarette smokers compared with non-smokers. There was a significant negative correlation between prolactin level and diastolic blood pressure (r=-0.22, p=0.003), but no interaction between prolactin and other cardiovascular risk factors.

Conclusions: Hyperprolactinaemia is present in a significant proportion of community psychiatric patients. Cigarette smoking appears to reduce prolactin levels, but further studies are needed to investigate the clinical significance of this finding. The mechanism(s) by which prolactin influences blood pressure in antipsychotic-treated patients also requires further investigation.
551. Prenatal Exposure to Herpesviruses and Neuropsychological Outcomes on Schizophrenia

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Background: Previous studies have demonstrated that exposure to maternal genital/reproductive infections are related to an elevated risk of schizophrenia. Neuropsychological anomalies in several domains, and neuromotor abnormalities, have been consistently observed in patients with schizophrenia and in subjects destined to develop this disorder. To date, however, the etiologies of these phenotypic outcomes are not well understood. Hence, we aimed to examine whether maternal exposure to these infections is related to neuropsychological abnormalities found in this disorder.

Methods: Exposure status was documented prospectively by analysis of archived maternal serum specimens for herpes simplex virus type 2 (HSV-2) and by physician diagnoses of other maternal genital/reproductive infections among cases of schizophrenia from a large birth cohort. In the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study, cases from this cohort were assessed as adults with a comprehensive neuropsychological test battery.

Results: Maternal genital/reproductive infections, including HSV-2, were associated with significantly diminished performance on several measures of verbal memory assessed by the California Verbal Learning Test and impaired neuromotor functioning, as assessed by the Grooved Pegboard test (p<.02) in cases with schizophrenia. These outcomes occurred in the context of preserved global intellectual functioning. Controls exposed to these infections also evidenced significant verbal memory and neuromotor deficits.

Conclusions: These findings suggest that maternal genital/reproductive infections may contribute to neuropsychological dysfunction observed in patients with schizophrenia. If these results are replicated, then available preventive measures may lead to improvement in neuropsychological capacity and possibly other functional outcomes in patients with schizophrenia. Supported by NIMH R01MH602749; 1K02MH66422; NARSAD.

552. Fetal Exposure to Maternal Stress Hormones and Risk for Schizophrenia: Preliminary Evidence of a Racial Disparity

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Background: Previous studies have linked stressful life events during pregnancy (e.g. death of a spouse) to increased risk for schizophrenia. Nevertheless, no study has explored the contributions of biological indicators of stress during pregnancy to risk for schizophrenia in offspring.

Methods: Participants were 58 schizophrenia cases and 98 controls from a large birth cohort that followed pregnant women from 1959-1967. Psychiatric diagnoses were determined through semi-structured interviews and medical records review. Controls were matched to cases based on date of birth, infant sex, length of time in cohort, and availability of maternal sera. Maternal cortisol was assayed from archived maternal sera from each trimester of pregnancy using immunofluorescence. Analyses used conditional logistic regression.

Results: Decreases in maternal cortisol during the second trimester of pregnancy were associated with an increased risk of schizophrenia (OR=1.04, p=.09). When restricting analyses to African Americans, fetal exposure to decreases in cortisol in the second and third trimesters, respectively, was related to a 1.22 (p=.09) and 1.08 (p=.09) increased risk of developing schizophrenia. There was no relationship between fetal exposure to cortisol and risk for developing schizophrenia among Caucasians.

Conclusions: Results provide preliminary evidence of a relationship between decreases in cortisol during pregnancy and risk for schizophrenia among African Americans. Decreases in cortisol during pregnancy have been observed in both PTSD and African American pregnant populations, the latter of which may represent stress associated with repeated exposures to racism. Although results only approached significance, they may potentially contribute to the previously observed racial disparity in schizophrenia.

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553. First Episode Schizophrenia and Bipolar Disorder Associated with Distinct Personality Trait Profiles

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Background: Personality is altered in chronic schizophrenia and bipolar disorder (Bagby RM et al, Psychiatry Res 1997; 70:83-94), but it is unclear whether these changes are present at first episode. The NEO-FFI is a 60-item self-assessment questionnaire that measures neuroticism (N), extraversion (E), openness (O), agreeableness (A) and conscientiousness (C). It has good reliability and cross-cultural validity (McCrae RR et al, J Res Person 2004; 38:179-201).

Methods: Clinically stable patients with first episode schizophrenia (22M,4F) and bipolar disorder (24M,8F), and psychiatrically healthy subjects (101M,36F) completed the NEO-FFI. Gender-specific T scores were analyzed.

Results: Age correlated significantly with all dimensions except E, so age was entered as a covariate in a MANOVA with personality scores as dependent variables and diagnosis as a fixed factor independent variable. Statistically significant effects were observed for age (F(5,187)=4.26, p=.001) and diagnostic group (F(10,376)=10.27, p=.000), and there were group differences for N, E, A, and C (all F(5,191)=9.40, p=.000). Post hoc contrasts showed schizophrenia and bipolar groups were similar on N (mean=59.2 vs 61.7, respectively), A (45.6 vs 43.3), and C (40.0 vs 40.0). Compared to patient groups, comparison subjects were significantly lower on N (43.6) and higher on A (52.2) and C (49.5). All groups differed significantly on E: schizophrenia subjects scored lowest (43.9), comparison subjects highest (57.0), and bipolar subjects scored intermediately (51.7) (all p < .014).

Conclusions: Personality deviations are present in first episode schizophrenia and bipolar disorder, and are similar to abnormalities previously described in patients with more chronic illness.

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554. Behavioral Characterization of Mice in Which BDNF Promoter-IV Driven Transcription is Impaired

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Background: Bdnf transcription is controlled by at least nine unique promoters, each driving expression of a short 5’ untranslated exon that is spliced to a common coding exon. The promoter upstream of exon IV is highly dependent on neuronal activation and calcium signaling. BDNF is important during development for survival and differentiation of multiple classes of neurons as well as mediating various forms of synaptic plasticity during development and in adulthood. BDNF has been implicated as a functional player in multiple forms of learning and memory and in the etiology of numerous neuropsychiatric disorders.

Methods: We generated promoter IV mutant mice (BDNF-KI-IV) by inserting a GFP-STOP cassette within the Bdnf exon IV locus, resulting in disruption of promoter IV-mediated Bdnf expression. We carried out a battery of behavioral tests to determine whether disruption of promoter IV-driven expression results in behavioral changes relevant for the study of neuropsychiatric disorders.

Results: We previously reported that these mice have a deficit in parvalbumin-positive neurons in the prefrontal cortex as well as impairments in inhibitory GABAergic signaling. These mice showed no baseline changes in either depressive- or anxiety-like behaviors. However, they do exhibit serious impairments in startle reactivity, prepulse inhibition and extinction of aversive conditioning.

Conclusions: Disruption of promoter IV-driven Bdnf transcription results in deficits in inhibitory interneuron signaling in the prefrontal cortex. These cellular phenotypes related to interneuron function are consistent with behavioral impairments in sensory hypersensitivity and sensory-motor gating as well as excessive perseveration as exhibited by an inability to mediate extinction to aversive conditioning.

Supported by NIMH Intramural Program

555. Copy Number Variation (CNV) of Selenium-Binding Protein (SELENBP)1 in Schizophrenia

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Background: Rare copy number (CN) mutations and mitochondrial dysfunction may play a role in the etiology of schizophrenia. Genome-wide screens for alleles of CN mutations cannot provide functional interpretation for the involvement of certain loci in the disease etiology. We combined the two etiological factors in a focused study of CN mutations in the mitochondria-related selenium binding protein 1 (SELENBP1) locus previously linked with schizophrenia hypothesizing that CN mutations in this locus alter the gene product’s activity in patients.

Methods: We analyzed SELENBP1 CN variation (CNV) in a) blood from 49 schizophrenia patients and 49 healthy controls, in b) postmortem cerebellar samples from 14 schizophrenia patients and 14 unrelated matched controls and in c) blood from 26 trios of schizophrenia probands and their healthy parents using real-time PCR.

Results: SELENBP1 locus CN was reduced in four patients but none of the controls of cohort a). Since CN of genes vary among tissues we investigated SELENBP1 CN in postmortem brain samples (b). We found reduced CN of the SELENBP1 locus in two patients and none of the controls. Since CNV may either be de-novo or inherited we analyzed CNV of the triads cohort (c). Three patients exhibited drastic CN reduction not present in their normal parents (de-novo mutation, as analysed in the figure). Postmortem cerebellar SELENBP1 mRNA levels were reduced.

Conclusions: We present recurrence of decreased CN of the SELENBP1 locus in three unrelated patients’ cohorts but not in the controls suggesting functional involvement of these mutations in the etiology of schizophrenia possibly contributing to mitochondrial dysfunction in this disorder.

556. Age at Onset of Schizophrenia and Volume Reduction in Orbitofrontal Gyrus are Associated with UF1DL Polymorphism

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Background: The 22q11.2 deletion is a known genetic risk for schizophrenia. UF1DL gene is located at this region and it seems to be associated with neurodevelopment. A UF1DL SNP, rs5992403, was associated with schizophrenia, but thereafter were conflicting results. The aim of this study was to evaluate the association between rs5992403 polymorphism with age at onset of schizophrenia and cortical volumes assessed by MRI.

Methods: A total of 145 patients with schizophrenia were recruited from the Schizophrenia Program of UNIFESP. Each patient was assessed and diagnosed by two psychiatrists according to OSM-IV and genotyped for rs5992403 polymorphism by TaqMan probe-based real-time PCR assay. Fifty-eight patients, divided into groups according to their genotypes, underwent MRI scan in a 1.5T scanner. A whole-brain gray matter voxel-based morphometry (VBM) analysis was performed using SPM5. Smoothed images (FWHM=10mm) were analyzed through a factorial ANCOVA design using intracranial volume as a covariate. Small volume correction (SVC) was used for multiple comparisons at p<0.01 (false discovery rate).

Results: A-allele carriers had an earlier age of onset than G-allele carriers from 14 schizophrenia patients and 14 unrelated matched controls and in c) blood from 26 trios of schizophrenia probands and their healthy parents using real-time PCR.

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B I O L  P S Y C H I A T R Y  2 0 1 0 ; 6 7 ; 1 8 - 2 7 1 8  1 6 1 5
(A-allele=23.25±6.91; G-allele=24.94±7.46; p=0.047). Moreover, the frequency of A-allele was higher in the early-onset schizophrenia group (age of onset ≤ 18 years) (p=0.036). A significant volume reduction in the left orbitofrontal gyrus (MINI x,y,z= -29.19 -15) was observed in the AA group (Z=3.91, psvc(500mm3) = 0.01) in comparison to GG group.

**Conclusions:** These data suggest that UFDNL polymorphism may play a role in brain morphology and also in the age at onset of schizophrenia.

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557. Neurodevelopment in Adolescence and Young Adulthood (NAYA): Relationship Between Prodromal Symptoms and Self-Reported Schizotypal Symptoms in Youths At-Risk for Psychosis

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**Background:** In the past decade, increasingly widespread efforts have aimed at identifying young people at risk for psychosis. Although interview based methods have become the gold standard for classifying risk status, multidimensional self-report measures may be useful adjuncts for the examination of quantitative endophenotypes associated with propensity for psychosis.

**Methods:** In the context of our ongoing NAYA longitudinal research program examining candidate endophenotypes in at-risk youths, individuals at clinical and/or genetic risk for psychosis (AR, n=21, mean age=19.5), low risk for psychosis (LR, n=33, mean age =20.6), and patients with psychosis (n=9, mean age =21.9), were administered the Structured Interview for Prodromal Syndromes (SIPS) and a computerized version of the Schizotypal Personality Questionnaire (SPQ).

**Results:** Groups did not significantly differ in age, education or parental education. SPQ validity scales (Lie, Defensiveness) were within normal limits for all groups, suggesting participants answered truthfully and without attempting to deny problems. Multivariate analysis of variance (MANOVA) of SPQ responses yielded a highly significant effect of group (p<.001), with post-hoc analyses revealing greater endorsement of schizotypal signs and symptoms across all three SPQ factors (Cognitive-Perceptual, Social-Interpersonal, Disorganization) by revealing greater endorsement of schizotypal signs and symptoms across all three factors (Cognitive-Perceptual, Social-Interpersonal, Disorganization) by groups than by the LR group (all p’s <.05). Within the SPQ factors (Cognitive-Perceptual, Social-Interpersonal, Disorganization) by revealing greater endorsement of schizotypal signs and symptoms across all three SPQ factors (Cognitive-Perceptual, Social-Interpersonal, Disorganization) by

**Conclusions:** A multidimensional self-report measure can characterize schizotypal features in youths at-risk for psychosis, and may therefore assist investigations of the relationship between clinical features and quantitative candidate endophenotypes of psychosis.

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558. Lithium Modulation of Gene Expression in Bipolar Disorder

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**Background:** Genetic studies in bipolar disorder (BD) have identified a wealth of candidate loci with limited replication between studies, indicating high heterogeneity among samples. We have focused on BD patients who are excellent lithium responders and performed a linkage study followed by gene expression in post-mortem brains. These studies identified several genes in regions linked to BD that are differentially expressed in BD patients compared to controls. Since these candidate genes were ascertained through a lithium-responsive cohort, we sought to determine if lithium modulates their expression.

**Methods:** Long-term lithium treatment assays were performed in several brain-specific cell lines and gene expression changes were quantified using real-time PCR. Additionally, lithium treatment assays were performed in B-lymphocytes from BD patients classified as excellent lithium responders, non-responders, as well as controls.

**Results:** The expression of several synapse-related genes was found to be influenced by lithium treatment. Of these, SYN2 (Saposin II) was of particular interest, as it was significantly upregulated by lithium in cell culture - which replicated our previous findings in post-mortem BD brain samples. Another interesting gene, MAG1 (Membrane-associated guanylate kinase, WW and PDZ domain-containing protein 1) was similarly influenced by lithium.

**Conclusions:** By focusing on lithium-responsive BD we have identified several synapse-related genes that seem to contribute to the etiology of BD and lithium response. By investigating lithium’s role in modulating gene expression, we may help characterize the pathways altered in BD.

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559. Association of Plasma Dopamine β-Hydroxylase and Variants at the DBH Gene with Differences in Factor Scores Representing Clinical Features of Schizophrenia

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**Background:** Dopamine beta-hydroxylase (DBH) converts dopamine to norepinephrine, and occurs in human plasma, where its activity is genetically regulated. Prior studies suggest that variation in plasma DBH activity associates with differences in the presentation of schizophrenia, although not with risk for schizophrenia per se. Plasma DBH activity strongly associates with specific variants at DBH, including rs1611115 in the 5’ region, and a nonsynonymous single nucleotide polymorphism (SNP) in exon 11, rs6271 (arg355cys). The present study examined associations of plasma DBH activity and SNPs at DBH with factor scores reflecting different aspects of schizophrenic symptomatology.

**Methods:** Plasma samples on 128 patients from pedigrees in the Maryland Epidemiological Study of Schizophrenia were assayed for DBH enzyme activity. DBH SNP rs16111122 was available from the Illumina version 4 linkage marker set, while rs1611115 and rs6271 were typed on the Taqman platform. Factors derived as described by McGrath et al. (2009, Arch. Gen. Psychiatry 66: 591) were tested for association with DBH activity and each DBH SNP, using ASSOC in S.A.G.E.

**Results:** Several factors showed significant associations, including Hallucinations (associated with DBH activity, p = 0.003). Positive symptoms (associated with rs6271 only, p = 0.04) and the Affective factor (associated with both DBH activity and rs1611122, p=0.006 and 0.02 respectively).

**Conclusions:** The current results are consistent with prior literature suggesting that variation in plasma DBH associates with differences in the presentation of schizophrenia, and supports the hypothesis that DBH is a modifying gene in schizophrenia.

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560. Cross-Phenotype Analysis of 380 Candidate Gene Markers in Schizophrenia: Evidence of Genetic Effect on the Age at Onset

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Background: Despite the considerable amount of data from genetic case-control studies in schizophrenia, none of the genetic association studies have compared the strength of the genetic associations across different phenotype related to schizophrenia.

Methods: The aim of this study is to assess the overall genetic effect on different severity phenotypes associated with schizophrenia using 380 SNPs form genes implicated in the neurobiology of schizophrenia. The severity phenotypes that we investigated in this study are the following: lifetime suicide attempt, age at onset, alcohol use disorder comorbidity, drug use disorder comorbidity, nicotine addiction and resistance to antipsychotic treatment.

Results: We analyzed 154 schizophrenic patients from White European ancestry recruited in Toronto at the Centre for Addiction and Mental Health. Thirty-four patients who had a psychotic onset when they were younger than 22 (optimal cut-off from admixture analysis) were considered early onset schizophrenics. Furthermore our data showed that the cocaine- and amphetamine-regulated transcript (CARTPT) is associated with early onset in schizophrenia. The SNP with highest p-value was the SNP rs10515115 (p=0.0007).

Conclusions: Our analysis of 380 markers across candidate genes revealed that the age at onset is the phenotype that overall showed the strongest genetic effect compared to the other phenotypes explored in this study. In conclusion the age at onset is a promising phenotype for the ongoing psychiatric genetic studies.

Supported by NARSAD

561. Tag-SNP Based Study of 109 Candidate Genes for Schizophrenia Selected Using an Evidence-Based Prioritization Algorithm


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Background: Introducing evidence from multiple domains may be useful in prioritizing genes for subsequent testing.

Methods: We ranked all known genes (n=3820) under several linkage peaks in the Irish Study of High-Density Schizophrenia Families using three different evidence domains; 1) a meta-analysis of microarray gene expression results using the Stanley Brain collection, 2) a schizophrenia protein-protein interaction network, and 3) systematic literature searching. Each gene was assigned a domain specific p-value and ranked after evaluating the evidence within each domain. For Protein-Protein Interaction, the steps from the schizophrenia susceptibility genes a) DTNBP1, b) NRGI, and c) Ak1 in Protein-Protein Interaction databases were determined, respectively. For Literature Searches, Pubmed was systematically searched using all 3820 genes with 40 schizophrenia-related search terms. For a final ranking of these genes, we summed the -log10 of their p-values on each of these five variables (or Q-values in the case of Gene Expression). In addition, any gene with Gene Ontology terms that included “nervous system development” or “brain development” was also selected. Approximately 3000 SNPs from a custom Illumina iSelect genotyping array using the Infinium assay were allocated to evaluate the top ranked genes. After assigning all LD tagging SNPs in the most highly ranked genes, they were investigated using 2,849 SNPs.

Results: No individual SNPs were significant after Bonferroni correction, which may be too stringent. However, a number of genes contained clusters of SNPs with p<.01, indicating highly suggestive associations. These included PRKGI, VAV1, PRKCE, and CNTN4.

Conclusions: Our results could be consistent with recent evidence across many complex disorders demonstrating many small effects across the genome. Supported by VA Merit Review Program

562. Association of DISC1 Genetic Variation with Intermediate Phenotypes in Neuroimaging: Replication and Further Extension

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Background: DISC1 has been linked to the risk for major mental illness. Several studies, which assessed the effects of the DISC1 gene on cognition as well as on brain structure and function, have led to partly inconsistent results. The aim of this study was to re-investigate the effects of the DISC1 Ser704Cys locus on cognition, regional brain volumes and MRS parameters in human subjects.

Methods: Overall 232 subjects participated in the study. Subjects were genotyped with respect to the rs821616 SNP of the DISC1 gene and underwent magnetic resonance imaging (MRI) and spectroscopy (MRS). MRI data were analyzed using both manual volumetric assessment of regions of interest and voxel-based morphometry (VBM) as implemented in SPM5.

Results: Manual volumetric assessment, but not VBM revealed a significant effect of the DISC1-SNP rs821616 on hippocampus volume with Ser homozygotes having lower relative right hippocampal volume compared with Cys carriers. No significant genotype effects were found on MRS parameters in the left hippocampus, frontomedian cortex and middle frontal gyrus, whereas VBM showed significant effects bilaterally in the middle frontal gyrus as well as in right parietal cortex with Ser homozygotes having lower gray matter volumes in these cortical regions. Ser homozygotes also revealed lower performance in working memory tasks.

Conclusions: The present results in part replicate prior findings of DISC1 gene effects on hippocampal volumes, and provide evidence for further associations of the DISC1 Ser704Cys locus with other intermediate phenotypes such as regional prefrontal gray matter volumes and working memory performance.
563. A Multimodal Assessment of the Genetic Control over Working Memory

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Background: Working memory (WM) performance is significantly influenced by genetic factors, however the biological mechanism through which variance in WM is transmitted is unknown. Given that WM relies on a large-scale distributed network of brain regions, we employed a multimodal approach to assess heritability of the integrity of white matter tracts and gray matter density in regions associated with WM as well as to performance on a battery of WM tests.

Methods: We assessed genetic contributions to both WM performance and to neuroimaging measures focused on the network of brain regions associated with WM in 467 individuals from extended families. Imaging measures included DTI indices in major white matter tracts and MRI measures of frontal and parietal gray matter density. Analyses directly addressed whether WM performance and neural structural integrity are influenced by common genetic factors (e.g. pleiotropy).

Results: While all cognitive measures, gray matter regions, and white matter tracts assessed were significantly heritable, only performance on a spatial delayed response task and integrity of the superior longitudinal fasciculus exhibited shared genetic factors.

Conclusions: This finding may inform our understanding of how variation in WM performance may be genetically transmitted. As WM may be a core component of other, higher level processes, this also has more widespread implications for the heritability of complex cognitive functions. Furthermore, this work may particularly inform our understanding of transmission of cognitive deficits in disorders for which WM impairment is a known endophenotype, such as schizophrenia.

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564. The Replication of Egr3 as a Potential Susceptibility Gene for Schizophrenia in Korean Patients with Schizophrenia

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Background: Early growth response (Egr) genes play critical role in signal transduction in the brain, which is involved in neuronal activation, brain development, and synaptic plasticity. Egr3, a member of Egr gene family, resides at the chromosomal location 8p21.3 and was suggested as a potential susceptibility gene in schizophrenia from study with Japanese population, which requires further replication with an independent sample.

Methods: We investigated the association of Egr3 and Egr2 genes with schizophrenia in Korean patients with schizophrenia. Along with 350 healthy individuals, a sample of 244 schizophrenia was analyzed.

Results: Among examined four SNPs of Egr3, SNP3 in the intron1 of Egr3 gene showed significant association with schizophrenia (P = 0.0008, Chi2 = 11.156, OR = 1.493). In addition, ‘T-G-C-G’ haplotype of Egr3 was under-presented in the patients with schizophrenia (P = 0.0073, Chi2 = 7.188, OR = 0.697).

However, association between SNPs of Egr2 and schizophrenia was not found.

Conclusions: These findings are in consistent with the previous genetic association of Egr3 gene in Japanese cohorts, which could suggest Egr3 as a compelling susceptibility gene in schizophrenia.

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565. A Schizophrenia Risk Gene, ZNF804A, Influences Neuroanatomy and Neurocognition

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Background: A SNP in ZNF804A (rs1344706) has emerged as a risk factor for schizophrenia. This SNP has been associated with abnormal patterns of neural connectivity in functional MRI, but has not yet been studied with structural MRI or standard neurocognitive measures.

Methods: We assessed the relationship of rs1344706 to brain structure in a subset of controls (n=39) with structural MRI (1.5T GE scanner, standard SPGR acquisition). To maximize sample size, carriers of the minor allele (n=21) were grouped and compared to T allele homozygotes (n=18). In a larger subset of healthy controls (n=169), we tested the effect of T allele dosage on neurocognitive performance as assessed by the Trailmaking Test, Part A (Trails A).

Results: Consistent with the dysconnectivity hypothesis, T allele homozygotes displayed larger total white matter volumes (p<.05) than nonhomozygotes. In voxelwise analysis using SPM5, risk-allele homozygotes demonstrated relatively reduced gray matter volumes in several regions comprising the default mode network, including angular gyrus, parahippocampal gyrus, posterior cingulate, and medial orbitofrontal gyrus/gyrus rectus (FDR-corrected p<.05). These gray matter deficits correlated with impaired performance on Trails A (n=31, p<.05). In a larger, independent cohort of healthy controls (n=169), T allele dosage also predicted impairments on Trails A (p<.05).

Conclusions: Taken together, these results support the hypothesis that rs1344706 promotes risk for schizophrenia via effects on neural connectivity, contributing to neurocognitive deficits and psychotic symptomatology.

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566. Impact of PLA2 Gene Polymorphisms on Onset of Schizophrenia and Illness Severity

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Background: Phospholipases A2 (PLA2) are suspected to be involved in the pathology of schizophrenia; positive association has been found in Chinese, Korean and Brazilian population. We tested whether risk for schizophrenia in Croatian population was associated with allelic and genotype frequencies of single nucleotide polymorphisms (SNPs) in three genes of PLA2 superfamily:

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567. Allelic Variations in ANK3 and CACNA1C Impact on Spatial Working Memory, Startle Reactivity and Personality Traits in Healthy Males

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Background: Recent genome-wide association studies have reported strong evidence that genetic variants within CACNA1C and ANK3 are risk factors for bipolar disorder. Moreover, the CACNA1C gene contributes to the etiology of schizophrenia and major depression. The impact of these polymorphisms on cognition and personality traits is still unknown.

Methods: CACNA1C rs10606737 and ANK3 rs10994336 polymorphisms were analyzed in 530 healthy males, phenotyped for acoustic startle and prepulse inhibition, neurocognitive tasks and personality dimensions from the Eysenck Personality (EPQ), Tridimensional Personality (TPQ), State-Trait Anxiety (STAI), Schizotypy (STQ) and Behavioral Approach/Inhibition System (BIS/BAS) questionnaires. QTPhASE from the UNPHASED package was used for the association analysis of allelic data, with p values corrected for multiple testing by running 10000 permutations of the data.

Results: The rs10606737 A-allele was associated with lower EPQ extraversion, higher TPQ harm avoidance and STQ paranoid ideation (p<0.001) and higher STAI (p<0.01) scores. The rs10994336 T-allele was associated with more errors in the presence of the PL2G6-A-T and absence of the PL2G6-A-T allele. The presence of PL2G6-A-C, alone, or synergizing with PL2G6-C-T allele increased symptom severity only in males. PL2G6-A-A2, alone, in combination with PL2G6-A-C or PL2G6-G-T tended to decrease symptom severity.

Conclusions: SNPs: rs1549637, Ban1 and rs4375, alone and in combination may contribute to variable clinical expression of schizophrenia, possibly by modulating PLA2 expression/activity.

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568. Myelin Associated Glycoprotein Gene Influences White Matter Phenotypes in Schizophrenia

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Background: Oligodendrocyte and myelin related (OMR) genes are implicated in schizophrenia, particularly in frontal and temporal cortex. Magnetic resonance diffusion tensor imaging (DTI) studies have implicated frontal-temporal white matter tracts in schizophrenia. No study has linked these genetics and imaging findings in vivo. Here, we examine the relationship of the myelin associated glycoprotein (MAG) gene with white matter phenotypes within and between frontal and temporal cortex.

Methods: Eighty-five subjects (44 controls, and 41 schizophrenic) (age range 22-65) completed all protocols. DTI and MRI protocols were completed; for DTI 23 directions, 2 b=0 images, and 3 repetitions of the entire sequence were performed. Whole brain tractography, segmentation and measurement (fractional anisotropy) of the left and right uncinate, arcuate, and cingulate fasciculi was performed. For MRI, automated measures of left and right frontal and temporal white matter lobe volumes were extracted. For genetics, each individual was genotyped at the MAG rs720309 single nucleotide polymorphism.

Results: Following repeated measures ANCOVA a white matter tract by diagnosis by MAG genotype interaction was shown (F = 2.44, p<0.034), where specific effect was shown at the left arcuate fasciculus (F=9.25, P<0.003). For white matter volumes, a region by diagnosis by MAG genotype interaction (F=5.38, p<0.009), with significance in left (F=7.0, P<0.01) and right frontal white matter (F=6.2, p<0.05).

Conclusions: The MAG gene influences white matter phenotypes in schizophrenia. The MAG gene may be differentially regulated in schizophrenia compared to controls. Future work should continue to investigate the genetic underpinnings of white matter disruption in schizophrenia.

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569. Association Analysis of Polymorphisms on Nogo-66 Receptor (RTN4R) Gene with Schizophrenia in the Korean Population

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Background: Nogo-66 Receptor (RTN4R) gene was evaluated as a potential candidate for the risk of schizophrenia in previous studies. RTN4R is located in Chr 22q11 locus which is known as psychosis critical region. RTN4R is a glycosylphosphatidylinositol (GPI)-linked protein with multiple leucine-rich repeats that binds to Nogo-66, a myelin associated protein, which inhibits the outgrowth of neuritis and nerve terminals.

Methods: We investigated the association of five single nucleotide polymorphisms on RTN4R gene (rs665780, rs701427, rs696880, rs1567871 and rs701421) with schizophrenia in the Korean population. We genotyped five SNPs on RTN4R gene in 354 patients with schizophrenia and 394 normal controls from the Korean population. Then we compared the differences of genotype and allele distributions of the four polymorphisms between the two groups by logistic regression analysis.

Results: There were no significant difference of genotype and allele distributions

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of the five polymorphism on RTN4R gene between the schizophrenia patients and normal controls. In the analysis of haplotypes, there were significant genotypic differences of h4 distribution in codominant model (p=0.01, OR=0.54) and in dominant model (p=0.009, OR=0.51). There was significant allelic difference of h4 distribution (p=0.02, OR=0.56) if age and sex were regarded as covariate variables. Our data need to be interpreted with caution but it provides weak evidence of the involvement of RTN4R gene in the vulnerability to schizophrenia.

Conclusions: Our results demonstrate that polymorphisms on RTN4R gene might have influence on the risk of schizophrenia in the Korean population.

570. Association Analysis of Polymorphisms on Proline Dehydrogenase (PRODH) Gene with Schizophrenia in the Korean Population

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Background: Studies examining the association of polymorphisms on proline dehydrogenase (PRODH) gene with schizophrenia in cohorts of various ethnic origins have recently been reported. Proline has multiple physiological functions, one of which is as an inhibitory neurotransmitter and/or as a metabolic precursor of glutamate in subpopulations of glutamatergic neurons. PRODH encodes proline oxidase (POX), a mitochondrial inner-membrane enzyme expressed in kidney, liver and brain. PRODH gene comprises 15 exons that span 23,777 kb, located at 17.3 Mb in Chr. 22q11 locus which is known as psychosis critical region. It has been reported that -50% of the 22q11 deletion syndrome patients are hyperprolinemic, whereas 30-45% of them present with mental retardation and 12-30% have psychosis.

Methods: We investigated the association of four single nucleotide polymorphisms on PRODH gene (1195C>T, 1766T>C, 1852A>G and 1945T>C) with schizophrenia in the Korean population. We genotyped four SNPs on PRODH gene in 354 patients with schizophrenia and 395 normal controls from the Korean population. Then we compared the differences of genotype and allele distributions of the four polymorphisms between the two groups by logistic regression analysis.

Results: There were significant differences of genotype distribution of the 1945T>C polymorphism (p=0.04) and allele distribution of the 1766T>C polymorphism on p=0.03 of PRODH gene between the schizophrenia patients and normal controls. Our data provides weak evidence of the involvement of PRODH gene in the vulnerability to schizophrenia.

Conclusions: Our results demonstrate that polymorphisms on PRODH gene might have influence on the risk of schizophrenia in the Korean population. Supported by Soon Chun Univ. Research Fund

571. GABA System Genes in Tardive Dyskinesia

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Background: Reduced GABA activity has been hypothesized pathophysiological mechanism of tardive dyskinesia (TD), and a recent genome-wide association study identified a number of GABA system genes to be associated with TD in a sample of Japanese schizophrenia patients. We aim to explore GABA system genes for possible association with TD.

Methods: Our sample consists of 196 schizophrenia patients of European ethnic origin with TD assessment using the Schooler and Kane criteria (79 with TD). We genotyped single-nucleotide polymorphisms in the GABA receptor subunit genes: GABRA1, GABRA3, GABRA5, GABRA6, GABRG2, and GABBR1 using commercially available assays, and we analyzed the genotypes and alleles for association with TD.

Results: We found rs389292 in the GABRA3 gene to be associated with TD occurrence. Results for the other tested GABA gene polymorphisms were not significant.

Conclusions: Our results suggest that the GABRA3 gene may be associated with TD. We will be assessing other polymorphisms in GABRA3 in addition to other GABA system genes to further investigate the GABA hypothesis of TD. Supported by CIHR MOP

572. Sex-Specific Association of ZNF804A with Schizophrenia

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Background: The ZNF804A gene has been associated with schizophrenia in a genome-wide association study (O’Donovan, 2008). The SNP rs13447076 has been positive in several but not all further studies and a novel unlinked locus (rs7597593) was observed to be associated with schizophrenia in an independent Irish cohort. We performed a study of the novel locus and examined sex-specific genetic association and sex-gene interactions.

Methods: The genotype data were from two case-control cohorts in European (Scotland and Germany) and the USA GAIN cohort. Postmortem human brain mRNA expression data of normal individuals was generated by CBDB/NIMH. Sex-specific genetic association and sex-gene interactions were examined using logistic regression and the general linear model.

Results: rs7597593 was significantly associated with schizophrenia in women in all three cohorts: Scottish (OR=1.46, p=0.00896), German (OR=1.32, p=0.035) and the GAIN (OR=1.32, p=0.00898); however the significant association in men was found only in the Scottish sample (OR=1.25, p=0.04537). The weighted z-score combined p values indicated that association with this SNP is pronounced in women (p=0.0033), but not significant in men (p=0.3341). The association of this SNP with mRNA expression appeared to be marginal significant in women (p=0.0733, n=32), but not in men (p=0.147, n=78). There were significant effects of sex (p=0.0108) and sex-SNP interaction (p=0.006) on the ZNF804A mRNA expression.

Conclusions: We replicated the association of rs7597593 only in women, but not in men. The effect of sex and sex-SNP interaction on the mRNA expression in human brain may provide further evidence that the sex and sex-SNP interaction affect risk of schizophrenia.

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573. Meta-Analysis Provides Support for a Relationship between Genetic Variation in DTNBP1 and General Cognitive Ability

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Background: The dystrobrevin-binding protein 1 (DTNBP1) gene has been implicated in schizophrenia. Moreover, several studies have reported relationships between DTNBP1 and aspects of general cognitive ability in healthy volunteers, with less consistent reports in patient cohorts. We therefore examined the relationship between DTNBP1 variation and cognition in a large sample of non-psychiatric subjects via meta-analysis.

Methods: Medline search yielded 8 studies examining DTNBP1 variation and general cognitive ability, of which 6 had data available (total n=6719). The phenotype was defined as either the first principal component from multiple neuropsychological tests [general cognitive ability (g)] or full scale IQ. Seven SNPs had cognitive data available from at least 4 cohorts, and were thus meta-analyzed. For each SNP, the difference in cognition between major allele homozygotes and minor allele carriers was computed in Hedge’s g as the effect size (ES), which was pooled across studies using a fixed effect model.

Results: Pooled ES’s from 3 of the 7 SNPs were statistically significant (rs1018381, rs2619522, rs760761), ranging from -.084 to -.104, p’s<.01, with minor allele carriers demonstrating lower cognitive scores than major allele homozygotes. For one SNP (rs2619539), minor allele carriers demonstrated significantly higher cognitive scores (pooled ES = .123, p=.005). One SNP was also marginally significant (p=.071). No significant publication bias was detected.

Conclusions: Genetic variation in DTNBP1 modestly influences general cognitive ability in healthy subjects. These data are consistent with recent animal model work and suggest that DTNBP1 may be a component of a molecular pathway involved in human cognitive function.

574. Biomarkers of Oxidative Stress in Chronic Stabilized Patients with Schizophrenia and Euthymic Patients with Bipolar Disorder

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Background: Oxidative stress (OS) may contribute to the pathophysiology of schizophrenia (SZ) and bipolar disorder (BD). The aim of our study was to evaluate biomarkers of OS in patients with SZ and BD compared to healthy subjects.

Methods: Serum levels of a lipid peroxidation product, thiobarbituric acid reactive substances (TBARS), protein oxidative damage (carbonyl) and total non-enzymatic antioxidant potential (TRAP) were evaluated in 20 subjects with BD during euthymia, 55 chronic stabilized schizophrenics and 80 healthy volunteers. The diagnosis was in accordance to DSM-IV criteria.

Results: Serum TBARS and carbonyl levels were significantly higher in patients with SZ compared to either controls (p<0.0001), for TBARS and carbonyl levels) or euthymic patients with BD (p<0.0001, for TBARS and carbonyl levels) and, serum TRAP levels were significantly lower in patients with SZ compared to the BD and controls (p<0.0001, for both). No difference was found for TBARS, TRAP and carbonyl levels between controls and patients with BD. OS could be resultant from diminished levels of antioxidants or increased production of reactive species from oxygen or nitric oxide. The central nervous system (CNS) is extremely vulnerable to peroxidative damage. Since CNS is rich in oxidizable substrates; it has a high oxygen tension and a relatively low antioxidant capacity. OS markers show a state behavior in BD, however in SZ they seem to be trait markers.

Conclusions: Our results are in line with literature about SZ and BD concerning an initial severe deterioration in SZ, independent of the following episodes and, an episode-dependant pattern of deterioration in BD. Supported by CNPq

575. Biomarkers of Oxidative Stress in Early and Late Stages of Schizophrenia.

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Background: Schizophrenia (SZ) is a highly debilitating illness. Neuroimaging and postmortem findings, along with the behavioral and cognitive deterioration, could reflect a significant neurodegenerative process, probably most active in the early stages of the disease. Oxidative stress (OS) may contribute to the pathophysiology of SZ. The aim of this study was to evaluate biomarkers of OS in patients with SZ in early and late stages of disease compared to healthy subjects.

Methods: Serum levels of a lipid peroxidation product, thiobarbituric acid reactive substances (TBARS), protein oxidative damage (carbonyl) and total non-enzymatic antioxidant potential (TRAP) were evaluated in 80 healthy volunteers and 58 DSM-IV stabilized patients with SZ. 33 had a disease evolution of more than ten years and 25 had ten or less years of evolution.

Results: Serum TBARS, TRAP and carbonyl levels were significantly higher in patients with SZ compared to either controls (p<0.0001, for TBARS, TRAP and carbonyl levels). No difference between early and late stage groups were seen for TBARS (p=0.794) and TRAP (p=0.302). Significant increased levels of carbonyl were found in early stage group (p=0.031). Impaired antioxidant defenses and lipid peroxidation seem to be equally present along the SZ course. Since central nervous system is extremely vulnerable to peroxidative damage, higher levels of carbonyl in early stages could reflect one of the pathways of the time-limited aggression to the cell protein-content that may lead to permanent brain damage.

Conclusions: Our results of OS biomarkers are in line with literature concerning an initial severe and long-lasting deterioration, independent of the following episodes. Supported by CNPq
576. The Effects of Sleep Restriction on Daytime Performance: A Double-Blind Comparison of Eplivanserin, Placebo, or Temazepam

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Background: Impaired sleep due to sleep disorders, or lifestyle factors, is common and associated with medical and psychiatric comorbidities. Sleep restriction impairs daytime functioning, and results in increased morbidity and mortality due to accidents and illnesses. Slow wave sleep (SWS) is associated with restorative sleep, and impaired SWS has been observed in several diseases. Significantly, daytime cognitive function is positively associated with amount of SWS. Many hypnotic medications act via GABA receptors to improve sleep onset, but do not increase SWS. Eplivanserin increases SWS and improves sleep maintenance. This study will test the hypothesis that increased SWS will result in improved daytime performance in tests of attention, cognition and memory experimentally impaired by sleep restriction.

Methods: In a double-blind crossover, healthy 18-35yo subjects were administered eplivanserin and placebo (28-42 days each followed by 14-30 day washout periods), followed by a 6-day open-label comparison administration of temazepam. After each period, subjects completed 4-night sleep restriction. Cognitive, vigilance, and motor performance tasks, and subjective ratings of fatigue and mood were performed at baseline and before/after each sleep restriction period.

Results: 71 subjects were screened; 14 withdrew, and 26 were excluded due to sleep, medical or psychiatric criteria. 31 subjects were randomized; 27 completed the eplivanserin and placebo periods; 19 completed the temazepam period. Preliminary results from the pre- and post-sleep restriction examinations compared between conditions will be presented.

Conclusions: Reduced sleep impairs daytime performance, but function may be improved by experimentally increasing SWS. Supported by Sanofi-Aventis

577. Ambulatory Polysomnography to Investigate Obstructive Sleep Apnea (OSA) in Secondary Care Community Psychiatry Service Patients

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Background: Commonly used assessment questionnaires for sleep disorders have not been validated for use in psychiatric populations. Psychotropic medication can lead to weight gain, and obesity is a known predictor of obstructive sleep apnoea (OSA). Previous studies have reported a prevalence of OSA of ~20% in the background population. There are no studies investigating frequency of OSA in a generic psychiatric population.

Methods: Forty-three individuals were recruited from secondary care community psychiatric services in North East England. Demographic data, neck circumference, body mass index (BMI), blood pressure and medications were recorded, and the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Inventory (PSQI) were administered. Overnight home sleep studies recording. Respiratory movements, oxygen saturation and nasal flow data were collected to look for sleep apnoea and to determine the apnoea hypopnoea index (AHI). Results: OSA (AHI ≥5) was present in 47.7% of the sample (26.2% mild, 16.7% moderate and 4.8% severe). AHI correlated with age (r=0.52, p<0.001) and neck circumference (r=0.35, p=0.02). There was no significant interaction between AHI and ESS or PSQI scores. PSQI correlated with number of psychotropic drugs (r=-0.33, p=0.04) and ESS correlated with BMI (r=0.32, p=0.04).

Conclusions: Community psychiatric patients in North East England show higher rates of OSA than the general population. ESS and PSQI were not predictive of obstructive sleep apnoea in this population and may therefore have limited utility in patients with psychiatric disorders. Symptoms of sleep disturbance in this group may therefore be due to undiagnosed OSA. Supported by National Institute for Health Research

578. Screening for Obstructive Sleep Apnea in Psychiatric Outpatients

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Background: Obstructive sleep apnea (OSA) is reported at a higher frequency in psychiatric outpatients than in the general population. STOP is a new tool adopted by anesthesiologists to screen for OSA prior to surgery. We screened psychiatric outpatients for OSA using both the STOP and the ESS. We also screened for depression severity as measured by the Quick Inventory of Depression Symptomatology (QIDS).

Methods: 246 consecutively seen psychiatric outpatients were asked to complete the QIDS, the ESS, and the STOP apnea screening. Medication history, demographics, and a history of apnea were checked through a review of session notes, along with the results of available polysomnograms.

Results: 225 patients completed all 3 tests. Their average age was 53 (±14, range 19-92). 69% of patients were female, 31% were male. 121 patients had a diagnosis of unipolar depression, 70 patients had a diagnosis of a bipolar disorder, and 34 patients had another psychiatric diagnosis. 11% of patients were diagnosed with obstructive sleep apnea. The 4 question version of the STOP screening had 88% sensitivity and 69% specificity while the 8 question version had 92% sensitivity and 50% specificity in detecting OSA. A score of 10 or higher on the ESS had 40% sensitivity and 75% specificity for OSA. Patients with OSA scored significantly higher on the ESS (8.9 vs. 6.9, p<0.01) with the total QIDS score and the QIDS items dealing with sadness, concentration, general interest, low energy, and restlessness. Data related to the various medications used and diagnoses will be also presented.

Conclusions: This study duplicates earlier findings of higher frequency of OSA in psychiatric outpatients. Higher daytime sleepiness correlates with higher depression scores. The STOP screening tool for OSA has high sensitivity but low specificity for identifying OSA. It has a higher sensitivity but lower specificity than the ESS in detecting OSA.

579. Caffeine Reduces Behavioral Risk-Taking During Sleep Deprivation

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Background: Sleep deprivation lasting up to 2 nights has only minimal effects on risk-taking propensity. Furthermore, the effects of caffeine on risky behavior are negligible at short durations of sleep loss. Therefore, the effects of caffeine on risk-taking were examined over a longer duration of sleep deprivation (i.e., three nights) using a behavioral risk taking measure that requires the expenditure of effort (i.e., Balloon Analog Risk Task; BART).

Methods: Twenty-five healthy participants (21 men) between 20 to 35 years of age were deprived of sleep for 75 hours. Subjects received double-blind doses of 200mg caffeine (n=12) or placebo (n=13) in a chewing gum formulation bi-hourly from 0100-0700 each morning during the sleep deprivation period (i.e., total 800
mg/session). The BART was administered each morning at 10:20. Mixed-model analysis of covariance was used to analyze the BART Cost/Benefit Ratio.

**Results:** A significant drug x session interaction (p=0.002) was found. On the first two days of sleep deprivation, caffeine and placebo groups did not differ meaningfully, but by the third day (75 hours awake), the placebo group showed significant increases in risk-taking (p=0.01) whereas the caffeine group remained stable and was significantly lower in risk-taking than the placebo group (p=0.018).

**Conclusions:** Risky behavior was not affected by sleep loss of up to two nights duration. However, when extended to three nights, sleep deprivation was associated with greater risk-taking, but this increase was prevented by caffeine. Caffeine may provide some protection against risky behavior during conditions of extreme sleep loss.

**580. From Orexin Cells and Sleep Circuits to Clinical Therapy for Insomnia**

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**Background:** Orexins are neurotransmitters regulating arousal and reward behaviors, and signaling through the Orexin 1 Receptor (OX1R) and Orexin 2 Receptor (OX2R). Orexinergic neurons are a discrete population of cells localized within the hypothalamus, projecting widely to Orexin Receptor expressing regions. Dual and Selective Orexin Receptor Antagonists are being developed for the treatment of insomnia and other psychiatric indications in which the sleep/wake cycle is disrupted.

**Methods:** The pharmacological potency, selectivity, receptor occupancy and pharmacokinetic properties of structurally-diverse Dual Orexin Receptor Antagonists (DORAs) including the clinical development lead, MK-4305, were determined. Sleep promoting effects of DORAs were evaluated across species by sleep EEG and quantitative EEG (qEEG). In vivo characterization of DORAs in addiction and plasticity was studied with laser capture microdissection of sleep and reward nuclei in the brain to relate behavioral and transcriptional responses to Orexin Receptor antagonism.

**Results:** MK-4305 and other orally bioavailable DORAs effectively promote sleep across preclinical species including mice, rats, dogs and monkeys. Consistent sleep architecture and qEEG signatures were obtained for DORAs, and differed from those obtained with GABA modulators. DORA treatment inhibited behavioral sensitization to amphetamine and blocked amphetamine-induced transcriptional responses in Ventral Tegmental Area, Dorsal Raphe, Ventral Lateral Preoptic Area and Nucleus Acumbens. Pathways involved in amphetamine-induced synaptic plasticity were particularly impacted by DORA pretreatment.

**Conclusions:** DORA compounds effectively promote sleep and inhibit amphetamine-induced behavioral and transcriptional sensitization. These findings implicate Orexin Antagonists as demonstrating novel therapeutic potential for insomnia and the modification of addiction pathway plasticity in the brain. Supported by Merck.

**581. The Impact of Body Dysmorphic Disorder Comorbidity in Patients with Obsessive-Compulsive Disorder**

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**Background:**Obsessive-Compulsive Disorder (OCD) patients comprise a heterogeneous population that often presents additional psychiatric diagnoses. This study aimed to estimate the prevalence of body dysmorphic disorder (BDD) in a large clinical sample of OCD patients (DSM-IV) and to compare the demographic and clinical characteristics of patients with and without such comorbidity.

**Methods:** A cross-sectional design study with 901 patients from the Brazilian Research Consortium on Obsessive-Compulsive Spectrum Disorders (C-TOC). We studied several demographic and clinical variables, obtained by means of standardized instruments, like the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Dimensional Yale-Brown Obsessive Compulsive Scale (DY-BOCS), Beck Depression and Anxiety Inventories and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).

**Results:** BDD lifetime prevalence in our sample was 12.1%. OCD+BDD individuals were younger, more often single and unemployed, and presented more suicide ideation, planning, and attempts. They also had higher rates of comorbidity with major depression, dysthymia, social phobia, agoraphobia, simple phobia, post traumatic stress disorder, eating disorders, skin picking, Tourette syndrome, separation anxiety disorder and hypochondria, and more symptoms of sexual/religious, aggressive and diverse dimensions. Moreover, their Y-BOCS and Beck inventories scores were significantly higher. The comorbid group also presented earlier onset of OCD symptoms and lower insight.

**Conclusions:** BDD comorbidity has an important impact on the clinical presentation of OCD, with probable etiological and therapeutic implications. Supported by FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo, processo # 06/61459 7

**582. Childhood Family Function Predicts Dopamine Response to d-Amphetamine Challenge: A PET [¹¹C] Raclopride Study**

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**Background:** Children raised in aversive environments are at elevated risk for substance abuse problems. Animal models suggest that these early life stressors can lead to increased drug-induced dopamine responses in adulthood. To test
this hypothesis in humans we assessed whether individual differences in early family functioning would predict differences in amphetamine-induced striatal dopamine release.

Methods: Twenty healthy stimulant drug naïve subjects (age 20.5±2.2, 11 male) underwent two PET [11C]raclopride scans. Parametric t-maps of d-amphetamine (0.3 mg/kg, p.o.) vs. placebo scans were calculated. Change in signal was used to voxelsize linear regression against subscales of the Family Environment Scale. Two of these subscales, Moral-Religious Emphasis and Family Cohesion, predict vulnerability to addiction.

Results: d-Amphetamine administration significantly decreased [11C]raclopride binding potential (indicating increased dopamine binding) throughout the striatum. Regression maps identified bilateral clusters of correlation in the dorsal putamen for the Moral-Religious subscale (Figure 1: Left: 312 mm³ R= -0.71, p<0.05. Right: 304 mm³ R= -0.72, p<0.05). Subjects who rated their families as being less concerned with morality had larger dopaminergic responses to the test dose of amphetamine.

Conclusions: The results indicate that early family functioning influences dopamine responses to a first dose of d-amphetamine. Since striatal dopamine is thought to influence drug taking behaviour, this may identify a mechanism by which early life difficulties affect vulnerability to addiction.

Figure 1:

583. Orbitofrontal Volume, Decision-Making, and Cannabis Abuse in Adolescence

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Background: Development of prefrontal cortical systems during adolescence is thought to be importantly involved in the acquisition of decision making capacities. A diminished ability to anticipate the long-term consequences of substance abuse may contribute to substance abuse initiation early in life. We therefore investigated impulsivity and prefrontal volume in cannabis abusing (CA) adolescents and healthy control adolescents (HC)

Methods: Thirty-six subjects from the Salt Lake City area completed diagnostic interviews and drug screens. Structural imaging data was acquired on eighteen CA subjects (17.7 ± 0.9 years) and eighteen HC subjects (17.2 ± 0.8 years) using a T1-weighted 3D MPRAGE sequence on a 3T Siemens Trio magnet. Volumetric segmentation was performed with Freesurfer and adjusted volumes were obtained by taking the ratio of segmented orbitofrontal volumes to total segmented brain volume. The Barratt Impulsivity Scale (BIS) was used to assess impulsivity.

Results: CA subjects had significantly higher scores on the BIS planning subscale (p = .01), a measure of decreased future orientation. Compared to HC, CA also showed significantly decreased right medial orbitofrontal cortex (mOFC) volume (p = .01). Moreover, total mOFC volume was correlated with age of first use (r = -.5, p = .03).

Conclusions: The present findings support a relationship between impulsivity, developmental stage, cannabis abuse and mOFC volume. Cannabis abuse may contribute to altered OFC development since earlier age of first use was associated with smaller current volume. Moreover, increased impulsivity may contribute to or result from cannabis use.

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584. Response Inhibition in Healthy Individuals with a Family History of Alcoholism

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Background: Individuals with family histories of alcoholism show increased rates of addictions, including alcoholism. This increased risk may relate, in part, to poor ‘response inhibition’, a component of impulsivity proposed to contribute to the development and maintenance of addiction.

Methods: Healthy, non-alcoholic adults with (FH+, N=27) and without (FH-, N=28) a family history of alcoholism (in father plus other first-degree relatives) performed a Go/No-Go fMRI task where they were asked to press for ‘Xs’ (85% stimuli) and inhibit responding to ‘Ks’. Five impulsivity factor scores were calculated from behavioral and self-report measures using factor weightings derived from a previously published principal components analysis (Meda et al 2009). fMRI analyses of FH+ and FH- groups for successful inhibitions were performed using two sample t-tests and small volume correction within a priori regions of interest. Impulsivity factor scores were correlated with regions of interest BOLD signal.

Results: FH+ group displayed significantly greater BOLD signal than FH-(pFWEcorrected <0.05) during successful inhibitions in frontal regions (BA 9, 44, 45) and the left insula. Higher Self-reported Impulsivity Factor scores (BIS-11, Zuckerman Sensation Seeking Scale) significantly correlated with greater BOLD signal in the left insula, right anterior cingulate cortex and ventral striatum during successful inhibitions.

Conclusions: Individuals with a family history of alcoholism displayed differential brain activity during response inhibition in regions associated with self-rated impulsivity, despite absence of alcohol abuse. Abnormal neural systems involved in impulse control may contribute to vulnerability to addiction in individuals with family histories of alcoholism.

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585. An Interaction between Response to Reward in the Ventral Stratum and a Prodynorphin VNTR Polymorphism Predict Alcohol Consumption

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Background: Dynorphin signaling through kappa-opioid receptors can attenuate dopamine release in the ventral striatum (VS) thereby modulating reward-related processes such as alcohol consumption. We examined the moderating effect of a functional prodynorphin gene (PDYN) polymorphism on reward-related VS reactivity and self-reported alcohol consumption in 79 healthy, Caucasian volunteers. We focused on the 3- and 4-repeat alleles of a 68-bp PDYN promoter VNTR associated with relatively increased promotor activity.

Methods: PDYN genotype was determined using PCR amplification. Reward-related VS reactivity was assessed using fMRI. Poisson regression analyses were used to determine the effect of genotype and reward-related VS function on self-reported alcohol consumption.

Results: There were no main effects of genotype or VS reactivity on alcohol...
586. A Proton Magnetic Resonance Spectroscopy Investigation of Substance Induced Psychosis

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Background: Previous in vivo proton magnetic resonance spectroscopy (1H-MRS) studies have reported metabolite differences in patients at high risk of developing schizophrenia, chronic and first episode schizophrenia. At first episode however, it is often difficult to differentiate phenotypically substance induced psychosis (SIPs) from non-SIPs, compounded by the lack of reported biological markers that can aid with this differentiation. This research study sought to determine if these metabolite difference would be present in a drug using population with symptoms of psychosis.

Methods: 48 abstinent stimulant users were recruited from the community. Abstinence was ensured through a urinalysis. All participants were subjected to SCID and PANSS interviewing as well as a 3 Tesla 1H-MRS scan to measure in vivo metabolite levels in the medial prefrontal cortex.

Results: All subjects were cocaine and/or methamphetamine dependent but abstinent from all drugs for a minimum of 7 days. Subjects reported mild to moderate persistent psychotic symptoms as measured by the PANSS (total score = 41.96 SD 7.96). Spearman rho correlations revealed a negative association between N-acetyl aspartate (NAA)/Cr levels and PANSS positive scale scores (Spearman rho correlation coefficient = -0.38, p = 0.045).

Conclusions: This result is consistent with reports of reduced NAA in adolescents at high-risk of psychosis, those with a first episode of psychosis and those being treated for schizophrenia, suggesting that a substance induced psychosis may not differ biologically from schizophrenia.

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587. Lower Perfusion Detected with Arterial Spin Labeling in Young Abstinent Stimulant Abusers

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Background: SPECT studies have found lower brain perfusion in cocaine users, even after periods of abstinence. We used pulsed arterial spin labeling (PASL), a non-invasive MRI method for quantifying brain perfusion, to determine if perfusion abnormalities were detectable in young, abstinent stimulant abusers.

Methods: Nine adults (22 +/- 2.4 years) with a history of stimulant abuse (24.8 +/- 14.7 months) in an abstinence-based drug recovery program (length of abstinence 49.3 +/- 13.3 days) and nine comparison subjects (22.2 +/- 2.3 years) were examined on a Siemens TIM Trio scanner. Acquisitions included PASL (FAIR-QUIPPS-II), gree-fieldmaps, and T1 MPRAGE. PASL processing provided a relative perfusion map (rCBF) that was coregistered with the anatomical data. Tissue segmentation was performed with FreeSurfer. Bilateral FreeSurfer regions were combined to form frontal, parietal, cingulate, occipital and temporal lobe ROIs to sample the rCBF maps. A Welch’s t test was used to investigate group differences in the mean rCBF values of ROIs.

Results: Lower rCBF was found in all ROIs and was significant (p < 0.05) in the parietal, temporal and cingulate ROIs.

Conclusions: PASL detected lower rCBF in young abstinent stimulant abusers. Unlike SPECT, PASL does not involve ionizing radiation and therefore has the advantage that multiple measures can be performed in the same individual without the risk of radiation exposure. This ability to perform multiple measures should be useful for longitudinal studies of treatment and recovery where multiple measurements are needed.

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589. Amygdalar Volume Correlates with Depression in Marijuana Users

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**Background:** Mood alterations have been documented in long-term marijuana (MJ) users, and amygdalar volume reduction has been associated with depression and heavy MJ use. However, there are limited data examining the association between mood changes, MJ use, and amygdalar volume. This study examines the association between amygdalar volume and depression in MJ-abusing adolescents and adults compared to healthy controls (HC) to assess differences in self-reported measures of depression on amygdalar volume.

**Methods:** Twenty-two individuals with chronic heavy MJ use (aged 17.9±0.9 years) and 41 HC (aged 19.7±5.7 years) had a 3T MRI. Volumetric segmentation was performed with Freesurfer and amygdalar volumes were corrected for total brain volume. Subjects completed a diagnostic interview, Hamilton Rating Scale for Depression (HAM-D), and Profile of Mood States (POMS).

**Results:** Compared to HC, MJ users evidenced lower right amygdalar volume (p=0.008) when analyses were controlled for age. For MJ users, right amygdalar volume correlated negatively with depression (HAM-D, p=0.05), and age of first use correlated negatively with depression (p=0.02). Neither age of first use nor lifetime use was associated with amygdalar volume. Healthy controls evidenced no reduction in amygdalar volume and no correlation between right amygdalar volume and measures of depression or mood.

**Conclusions:** These findings suggest that reduced amygdalar volume may be associated with onset of MJ use. Further investigations into amygdalar volume and depressive symptoms in association with MJ use will need to be performed.

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590. Abnormal Error Processing in Current and Former Cocaine Users: An fMRI Based Study

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**Background:** Previous studies have demonstrated that specific regions including the anterior cingulate cortex (ACC), ventral prefrontal cortex, inferior parietal lobe ( IPL) and insula are functionally associated with response conflict or error processing. These regions are also identified as functionally impaired in impulsive substance abuse populations. The current study investigated error processing functionality in both former and current cocaine users together in a single statistical model. We expected to find both common and unique regional differences in the above groups in task relevant regions of an fMRI Go/No-Go task.

**Methods:** In the present study, 47 screened healthy controls, 30 former cocaine users, and 31 current cocaine users (age and sex matched) performed a Go/No-Go fMRI task. Data collected on a 3T scanner were preprocessed and analyzed using SPM2. Neural responses associated with correct rejections and false alarms were analyzed. An ROI based analysis was used to query specific apriori regions.

**Results:** Comparisons of activation associated with correct rejections showed no significant differences between former or current cocaine users and healthy controls. BOLD patterns associated with false alarms showed greater activity (p<0.05 uncorrected) in task-relevant regions including ACC, cuneus, insula, middle temporal, posterior cingulate, precentral, IPL, and middle temporal regions in both the current and former cocaine users compared to healthy controls.

**Conclusions:** This study extends and supports previous work that has shown differential neural activity involved in error processing between healthy individuals and cocaine users. It implies a dysfunctional “brake” system that may both predispose to and result from substance abuse.

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591. Altered Glutamate/GABA Relationship in the Cingulate of Marijuana Users

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**Background:** Given the widespread maturation of GABA receptors during the developmental period of adolescence, we hypothesized that exposure to cannabis may adversely modulate GABA transmission. The present study applied 1H MRS to measure changes in GABA and glutamate (Glu) concentration in the anterior cingulate cortex (ACC) of adolescent marijuana users compared with non-using controls.

**Methods:** Adolescents marijuana (MJ) users (N = 16; average age 17.8 years) and age-matched healthy control (HC) subjects (N = 21; average age 17.3 years) were scanned using a Siemens 3T Trio MRI system. Both a MEGAPRESS and a PRESS sequence were used to acquire metabolite and unsuppressed water 1H MRS data from a 22.5 mL voxel within the ACC. Within-voxel tissue-type segmentation did not reveal any significant differences in gray/white matter or CSF content between diagnostic groups. Spectra were fitted using LCModel and all metabolite integrals were normalized to the unsuppressed water integral (scaled; x10-10). Two-tailed t-tests were performed for GABA and Glu.

**Results:** The MJ cohort showed significantly decreased ACC Glu (MJ/HC = 2.35 ± 0.23/2.61 ± 0.45, P = 0.034) but not for ACC GABA (MJ/HC = 0.37 ± 0.017/0.38 ± 0.13 p =0.9) levels. The HC subjects showed a positive correlation between Glu and GABA (r=0.38, p=0.096) whereas MJ users showed a negative association (r=−0.25, P =0.35).

**Conclusions:** The difference between the correlation between GABA and Glu for the two groups approached significance (z score, p=0.075, 2-tailed). These finding infer impaired glutamatergic and gabaergic tone in adolescent MJ users.

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592. MDMA (Ecstasy) use is Associated with Increased Signal Intensity in Anterior Cingulate Gyrus during Flanker Task Performance: An fMRI Study

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**Background:** MDMA (Ecstasy) is a widely used recreational drug that produces serotonergic axon toxicity. Human MDMA users have impairments across a broad range of cognitive domains, including attention, concentration, psychomotor, and executive functions. MDMA use is associated with reduced gray matter concentration in the anterior cingulate gyrus.

**Methods:** We used fMRI at 3 T to examine anterior cingulate activation in abstinent human MDMA users (N=15) during performance of a modified flanker task that included a response inhibition and neutral condition. We examined task-evoked signal intensity in 3 subregions of the anterior cingulate: (Brodmann area [BA] 24, 25 and 32).

**Results:** We studied 5 male and 10 female users (average age, 24 years; lifetime MDMA use 40.77 +/- 92.92 episodes). In females only, task-evoked signal intensity in BA 24 and 32 correlated positively with lifetime MDMA use.
Combining a fMRI-Based Reward Processing Task and C11-Raclopride PET to Identify the Role of Ventral Striatal Dopaminergic Mechanisms in Reward Processing - Preliminary Data

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Background: Understanding the relationship between ventral striatal (VS) function and dopamine release may help to develop a potential biomarker for those at high risk for alcohol and substance use disorders, unipolar depression, bipolar disorder, and attention-deficit/hyperactivity disorder. Here we describe a potential method to probe this relationship.

Methods: Three healthy right-handed females, (age 23±2 years), underwent an fMRI scan during a monetary reward task and then three [11C]raclopride PET scans, each separated by a week: one at rest/baseline, one during a motor control task and one during the same monetary reward task as for the fMRI.

Results: There were significant VS fMRI BOLD signal changes, (25 voxels, MNI coordinates: 12, -3, 0, t = 42.02, corrected p = 0.02) to reward versus motor control task. There was also greater region-specific displacement of [11C]raclopride in the VS than other striatal regions to reward versus the motor control task, (VS = 2.53±0.08 to 2.45±0.07, Associative Striatum = 2.74±0.11 to 2.71±0.08; Sensorimotor striatum = 3.39±0.03 to 3.47±0.19). (There is insufficient power, at this stage, to demonstrate significance).

Conclusions: These preliminary results demonstrate the potential ability of this technique to measure physiological dopaminergic transmission in the functional subdivisions of the striatum and relate this to VS BOLD responses on the same task. Further subjects are currently being assessed using the same technique to confirm and expand this finding and develop an fMRI marker of striatal dopamine functioning.

Deficits in Perception and Motor Production of Facial Affect in Schizotypal Personality Disorder

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Background: Schizotypal personality disorder (SPD), is manifested by odd appearance and inappropriate affect. Whether these subjects compared with healthy controls (HC) had deficits in social reciprocity with respect to facial affect recognition and production was explored.

Methods: Subjects were recruited from the community, matched on age, parental socioeconomic status, IQ, and gender. Subjects (SPD= 55, HC=67) were asked to identify facial expressions. Two tasks to control for visual processing accuracy and speed were given. Subjects (SPD=22, HC=17) were asked to "make a happy face" while their photograph was taken. The process was repeated with the other basic emotions. Six raters viewed each separate facial expression and inferred which emotion was being expressed, as well as rated how confident they were of their guess, as well as how ambiguous, odd, attractive and approachable was the subjects' expression. Raters rated how comfortable they would be to meet the subject.

Results: SPD subjects compared with HC had more errors and were slower to identify facial emotions and had basic visual processing deficits. Although raters were able to correctly identify SPD subjects' facial expressions, raters were less confident in their guesses and found the expressions to be more ambiguous, more odd, less approachable, and less attractive. Raters were less likely to want to meet the SPD subjects.

Conclusions: SPD subjects may have primary visual processing deficits which compound their deficits in identifying facial affect. While they are able to display facial affect, it is not effective; raters did not want to meet them.

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Sub-Diagnostic Psychiatric Comorbidity Vs. Psychiatric Diagnoses in Alcoholism

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Background: Psychiatric comorbidity in substance use disorders is clearly established, however most studies ignore data on psychiatric symptom counts that do not meet criteria for a diagnosis. We examined psychiatric symptom counts and psychological measures in the domains of anxiety, mood and externalizing pathology in 48 long-term abstinent alcoholics (LTAA) compared to 48 age/gender comparable light/non-drinking controls (NC) and in 86 treatment naïve alcoholics (TxN) vs. 70 age/gender comparable light/non-drinking controls (NC).

Methods: Continuous measures of pathology (i.e., symptoms counts and psychological assessments) in each domain were compared between groups for: 1) all study participants, 2) excluding individuals with a lifetime psychiatric diagnosis in the domain, and 3) excluding individuals with a current psychiatric diagnosis in the domain.

Results: Psychiatric symptom counts and psychological pathology were greater in LTAA and TxN than NC. The differences between groups on these measures were not reduced by removal of individuals with lifetime or current diagnoses. In contrast, TxN had psychiatric diagnoses more similar to NC than LTAA.

Conclusions: The bulk of the difference between LTAA and TxN vs. NC in psychiatric illness was carried by sub-diagnostic psychopathology. In comparison to the limited view provided by using only symptomatology that meets criteria for a diagnosis, the use of continuous measures of psychiatric symptomatology and psychological abnormality yields a much more accurate picture of psychiatric illness co-occurring with alcoholism.

Supported by AA11311 and AA13659
596. Neuropsychology of the Schizo-Obsessive Subtype of Schizophrenia: New Findings
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Background: Interest in the neuro-cognitive profile of schizophrenia and co-morbid obsessive compulsive disorder (schizo-OCD) is rising in response to reports of high co-morbidity rates. Individuals with schizo-OCD appear more impaired than those with non-comorbid schizophrenia in several clinical domains including extra-pyramidal symptoms, and treatment strategies remain poorly researched. In a recent study, cognitive event-related potentials differentiated schizo-OCD from OCD and schizophrenia without OC symptoms, implying that schizo-OCD may represent a distinct clinical entity characterized by a distinguishable neurophysiology. Whereas schizophrenia has been associated with global disruption in a wide range of neuro-cognitive domains, OCD is associated with specific deficits featuring impaired performance on tasks of motor and cognitive inhibition involving frontostriatal neuro-circuitry.

Methods: Patients with schizo-OCD (n=12) were compared on a range of neurocognitive tasks with a schizophrenia group without OCD (n=15), matched for IQ, gender, age, medication, duration of illness.

Results: Patients with schizo-OCD made significantly more errors on a task of attentional set-shifting (ID-ED set-shift task). By contrast, no significant differences emerged on the Stockings of Cambridge task, the Cambridge Gambling Task or the Affective Go/NoGo tasks. No correlation emerged between ID-ED performance and severity of schizophrenia, OCD or depressive symptoms, consistent with neuro-cognitive impairment holding trait rather than state-marker status. Schizo-obssives also exhibited a trend toward more motor tics emphasizing a neurological contribution to the disorder.

Conclusions: Our findings reveal a more severe attentional set-shifting deficit and neurological abnormality that may be fundamental to the neuro-cognitive profile of schizo-OCD. The clinical implications of these impairments merit further exploration in larger studies.

597. Imaging and Cognitive Tasks in Clinical Interventions for Female-Specific Mood Disorders
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Background: Various lines of research have demonstrated that a significant proportion of women are more susceptible to develop depression during periods of intense hormonal fluctuation, such as postpartum and perimenopause. Here we prospectively examined the effects of antidepressant response on brain structure, chemistry and function using 3T MRI.

Methods: Drug-free, perimenopausal women on a major depressive episode and matched controls underwent a structural MRI. 2 fMRI scans looking at regulation of emotional conflict and working memory, and a 1H-MRS at baseline and at week 8. Patients with MDD were admitted to a 2-week single blind placebo run-in phase and non placebo responders received 8 weeks of treatment with and SNRI (Duloxetine or Desvenlafaxine).

Results: To date, 30 study participants have been recruited into these 2 clinical trials, including 15 subjects with MDD and 15 healthy controls. Structural, 1H-MRS and fMRI scans were performed at baseline with particular focus on exploring the fronto-limbic circuitry. We also expect to analyze changes in brain parameters and their relationship with treatment response.

Conclusions: We anticipate that the integration of imaging techniques and cognitive tasks into clinical trials of perimenopausal women with MDD will help uncovering underlying mechanisms that contribute to the development of mood changes and cognitive impairment in this sub-population, as well as the impact of antidepressant treatment on brain structure, chemistry and function. Supported by Eli-Lilly; Wyeth Pharmaceuticals; Canadian Institutes of Health Research; Father Sean O’Sullivan Research Centre

598. Arginine Vasopressin Influences on the Recognition of Social Words
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Background: Studies demonstrate that oxytocin has an important role in human social cognition and behaviour. There have been few studies exploring the effect of oxytocin nasal spray in clinical conditions characterised by social problems.

Methods: Patients with clinical disorders characterised by social deficit were recruited in a series of randomized double blind controlled trials.

Results: Results demonstrate that oxytocin nasal spray may enhance social cognition in clinical disorders.

Conclusions: Findings suggest potential of oxytocin nasal spray as a treatment for clinical disorders. Implications of findings and avenues for future research will be discussed.

Supported by National Health and Medical Research Council

599. Heart Rate Variability in Depression: Effects of Escitalopram
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Background: Depression is an independent risk factor for cardiovascular disease (CVD). A presumed mechanism underlying the high co-morbidity is reduced heart rate variability (HRV).

Methods: We sought to assess: a) whether HRV is reduced in patients with Major Depressive Disorder (MDD) compared to healthy controls; and b) whether MDD patients show normalization of HRV following escitalopram (ESC). No previous study of HRV with escitalopram has been reported. We have studied 25 MDD subjects and 25 matched healthy controls. MDD subjects received ESC for 12 weeks. We used the SphygmoCor software with a 3-lead ECG placement to derive the RR record over 10 minutes. Data was subjected to power spectral analysis and the time-frequency method, CardioBioBatch, to correct for respiration-related artifacts.

Results: There were no significant differences between MDD and healthy controls in either total amount of HRV or the LF:HF ratio of the power spectrum. However, significant alterations in HRV were noted in response to treatment with restoration of a 50:50 balance of the LF:HF ratio indicating a healthier cardiac function. LF was selectively depressed following treatment with greater mood improvement correlating with higher suppression of LF. RSA remained unchanged or tended to increase with ESC.

Conclusions: The findings are consistent with the Polyvagal Theory (Porges 2009) postulating that LF is mediated by unmyelinated vagal pathways and RSA is mediated by the myelinated vagal pathways. Mood stabilization correlates with improved HRV. Increased GABA modulation of brainstem areas via increased serotonin conserving RSA is an alternative explanation. Supported by Loyola University Stritch School of Medicine Intramural Grant

600. Carbon Dioxide Induced Panic in Schizophrenia with Auditory Hallucinations
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Background: Panic Disorder has been seen as unimportant and uncommon in patients with the severe diagnosis of schizophrenia. Recent observations raise the possibility that panic (and other anxiety disorders) may be an important part of schizophrenic psychopathology. Panic may emerge prodromally; contribute
to acute distress, disability, and specific psychotic symptoms; and predict medication side effects, regimen and response. It may predict significant benefit from adjunctive clonazepam. However, panic is easily missed in schizophrenia, due to limited clinician awareness, agitation, impaired cognition, and psychotic symptom overlap. It is vital to improve diagnostic methods.

Methods: Seven schizophrenic inpatients with auditory hallucinations (despite current antipsychotic medication) underwent a structured Panic and Schizophrenia Interview (PASI; which assessed panic symptoms concurrent with voices), followed by a carbon dioxide challenge test for panic (30 seconds of 35% carbon dioxide/65% oxygen).

Results: All subjects screened positive for concurrent panic and voices on the PASI. All subjects experienced acute panic anxiety to carbon dioxide but none to placebo. There were no unexpected adverse consequences. One subject had acute voices concurrent with induced panic (the only subject not on any antipanic medication). Clonazepam q12h was then openly added to her anti-psychotic, and dose was gradually raised until voices ceased clinically. Carbon dioxide rechallenge then produced neither panic nor voices.

Conclusions: This first systematic examination of panic induction in schizophrenia suggests that carbon dioxide challenge is safe and effective, that panic is prevalent in schizophrenia with voices, and that panic may sometimes be linked to voices. Further investigation is warranted.

601. Neural Predictors of Treatment Response in Major Depression using fMRI
Paul Keedwell
Cardiff University

Background: Previous follow-up studies indicate that increased visual cortical, ventral cingulated and subcortical responses of depressed individuals to sad facial stimuli, but not happy stimuli could represent reversible markers of disease severity. We hypothesized that greater responses in these areas to sad stimuli, but not happy stimuli, would predict better subsequent clinical outcome. We also explored areas that would predict a poor outcome.

Methods: Twelve melancholically depressed individuals in the early stages of antidepressant treatment in a secondary care setting participated in two experiments comparing responses to varying intensities of sad and happy facial stimuli, respectively, using event related functional MRI. They repeated the experiments after a mean delay of 12 weeks of treatment.

Results: There was a variation in response to treatment. Greater right visual cortex, parahippocampus and subgenual cingulate (BA25) responses to sad stimuli, but not happy stimuli, in the early stages of treatment were associated with a good clinical response (see Figure: positive predictors in hot colours; PH = Parahippocampus; SG = BA25). Greater ventrolateral prefrontal cortex (BA47/11) responses to either stimulus type were associated with a relatively poor outcome.

Conclusions: Right subgenual cingulate and visual cortical responses to sad stimuli predict good clinical outcome in the context of antidepressant treatment for severe depression in a psychiatric setting. Ventrolateral prefrontal cortex activity may indicate poor prognosis due to its relationship with negative rumination.

602. A Role for Oxytocin in the Acute and Long-Term Social Effects of Recreational Drugs
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Background: Recreational drugs have profound acute and lasting effects on social behavior. There is emerging evidence that oxytocin may play a role in these effects.

Methods: Acute and long-term effects of the popular party drugs MDMA ("Ecstasy") and GHB ("Fantasy") on affiliative behaviors in rats have been assessed using the social interaction test. Immunohistochemistry, autoradiography and gene expression studies have been used to examine associated changes in brain oxytocin systems.

Results: MDMA causes acute oxytocin release in rats via 5-HT1A receptor-mediated stimulation of neurons in the supraoptic and paraventricular nuclei of the hypothalamus. GHB also strongly activates these same hypothalamic nuclei. Various forebrain regions with high oxytocin receptor density were also activated by MDMA and GHB. This prosocial effects of MDMA in rats, and associated neuronal activation, were blocked by an oxytocin antagonist and by a 5-HT1A receptor antagonist. Long-term deficits in social behavior were evident weeks after rats had been exposed to MDMA, GHB, cannabis or methamphetamine. Chronic exposure to MDMA upregulated oxytocin mRNA in the hypothalamus while chronic GHB increased expression of oxytocin receptor mRNA. Chronic methamphetamine downregulated forebrain oxytocin receptor density. Ongoing studies are examining the ability of exogenous oxytocin treatment to reverse the adverse residual effects of these drugs on social behavior.

Conclusions: Oxytocin is worthy of further investigation as a mediator of both the acute prosocial effects of drugs and also their long-term adverse effects on sociability. There may be potential for oxytocin treatment to ameliorate long-term effects associated with drug use disorders in humans. Supported by NHMRC and ARC (Australia)

603. Age-Dependent Alterations of Astrocyte-Associated Intercellular Adhesion Molecule 1 Immunoreactivity in the Orbitofrontal Cortex of Older Subjects with Major Depression
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Background: Vascular and immune alterations in the prefrontal cortex may contribute to the etiology of major depression in elderly subjects. Since glial cells mediate immune and inflammatory responses in the brain, depression-specific immune alterations might be associated with glial cells in relevant regions of the prefrontal cortex. Intercellular adhesion molecule 1 (ICAM-1), a major inflammatory mediator in the vascular endothelium and astrocytes, could be altered in geriatric depression, but little is known about its age-dependent expression in subjects with major depression.

Methods: Immunohistochemistry for ICAM-1 and the astrocyte marker GFAP was applied to histological sections of the postmortem orbitofrontal cortex from 19 non-psychiatric control subjects and 18 subjects with major depression. Nine subjects in each group were over 60 years old. We measured the percentage of gray matter covered by ICAM-1 (area fraction of ICAM-1) in blood vessels and in extravascular accumulations of ICAM-1 immunoreactivity. Association of extracellular ICAM-1 to GFAP-positive astrocytes was investigated by double-labeling immunofluorescence.

Results: Both vascular and extravascular area fractions of ICAM-1 immunoreactivity were lower in depressives than in controls. Controls older than 60 experienced a dramatic increase in extravascular ICAM-1 immunoreactivity, but this increase was significantly attenuated in elderly MDD subjects. Most extracellular ICAM-1 immunoreactivity was coextensive
with GFAP-immunoreactive astrocytes.

Conclusions: There is a significant attenuation of extravascular and vascular ICAM-1 immunoreactivity in elderly subjects with major depression that might point to a specific alteration of astrocyte-associated immune function in the aging orbitofrontal cortex.

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604. Affective-Neurophilosophical Foundations of Depression and Cross-Species Emotional Endophenotypes

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Background: The recently emerged discipline of neurophilosophy focused on the translation of originally philosophical concepts into neuroscientific concepts which allow to empirically investigate the underlying neuronal mechanisms. An analogous problem is translation occurs in translational research where we have to translate the concepts used for the description of the animals and their functions into the ones employed to describe human nervous system function. The development of such bridge criteria with the possible need for correspondence and discrepancy between animal- and human-based concepts. The development of such bridge criteria with the possible need for bridge concepts is essential for successful translational research especially in psychiatry where the subjective-experiential component is so central.

Methods: Due to their different contexts, animal-based and human-based concepts can rarely be translated on a one-to-one basis.

Results: Hence in order to relate both kinds of concepts we need to develop criteria for correspondence and discrepancy between animal- and human-based concepts. The development of such bridge criteria with the possible need for bridge concepts is essential for successful translational research especially in psychiatry where the subjective-experiential component is so central.

Conclusions: My talk will focus on the development of such bridge criteria which will be exemplified by the example of translational research in depression. Supported by CIHR, EJLB Michael Smith

605. Aripiprazole Treatment of Co-Occurring Social Anxiety in Schizophrenia

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Background: Diagnosis and management of social anxiety may be important among patients with schizophrenia. Pharmacologic agents with serotonerceptor 1A agonist properties such as aripiprazole are believed to be effective anxiolytic drugs. This open-label study tested the hypothesis that aripiprazole would reduce social anxiety severity in schizophrenia, when compared to patients’ prior neuroleptic medications.

Methods: Outpatients with DSM-IV TR schizophrenia or schizoaffective disorder and co-occurring social anxiety disorder were cross-titrated from their first and second generation neuroleptic medications to a maximum 30 mg qd aripiprazole. Complete baseline assessments were also repeated monthly after 8 weeks. Patients who completed the initial 2 month study could enter a 6 month extension phase.

Results: Twenty-eight patients were enrolled in the short-term study, and 20 of them entered the 6 month extension phase. Last observation carried forward analysis showed significant improvements from baseline at month 2 and at month 12 in social anxiety scores (Liebowitz Social Anxiety Scale total, avoidance, and anxiety), social disability scores (Sheehan Disability Scale total, work, social life, and family), Lehman Quality of Life Interview scores (overall function, average life in general, and emotional well-being), psychosis (Positive and Negative Syndrome Scale total), and empathy quotient (Baron-Cohen and Wheelwright).

Conclusions: These findings suggest that the change to aripiprazole effectively improved social anxiety, psychosis, and quality of life in these patients. Improvements occurred within the 4 weeks of treatment and persisted when treatment continued for up to 12 months. Further studies are needed to confirm these findings in controlled trials.

Supported by CIHR, EJLB Michael Smith

606. Comorbid Panic Attacks and Schizophrenia: Implications for Symptoms and Cognition

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Background: Panic Disorder is a frequent comorbidity in Schizophrenia, but reported rates vary widely, ranging from 7.1% to 47.9%. There is conflicting data on the severity of positive and negative symptoms and incidence of depression, suicidality, and substance abuse, but schizophrenia severity appears to be worse in patients with panic syndromes. Although there are reports suggesting better insight in patients with panic, data on cognitive function is sparse.

Methods: The sample included 255 inpatient research subjects with Schizophrenia or Schizoaffective Disorder. They were assessed for anxiety using DIGS, symptoms using PANSS, and insight using SUMD. Cognition was assessed using a battery of neuropsychiatric testing.

Results: This sample had a prevalence of 15.3% for probable PD. The PD subjects had better awareness of mental disorder and of social consequences than patients without anxiety. They had higher full scale IQ, better scores on Wisconsin Card Sort Test, Animal Naming task, Trails A, and attention index of the Wechsler Memory Scale. There were no significant differences for PANSS positive or negative symptoms, however, the PD group did score higher for the PANSS dysthymia factor.

Conclusions: This may be the largest sample addressing the prevalence of PD in patients with rigorously diagnosed Schizophrenia and Schizoaffective Disorder having cognitive data. It demonstrates better cognitive function by several measures in patients with PD. These data support the possibility of a subgroup of patients with Schizophrenia-spectrum illnesses with comorbid PD who may benefit from treatment of their PD and whose illness may be amenable to novel treatment strategies.

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607. Animal Models to Investigate Biomarkers of Antidepressant Treatment Response

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Background: The identification of peripheral gene biomarkers (gene transcripts co-varying with disease states and treatment effects) is a primary goal in the treatment of major depression. Towards this goal, the recent demonstration that the unpredictable chronic mild stress (UCMS) rodent model recapitulates, not only the behavioral, physiological and molecular features of the human illness, but also the response to chronic antidepressant exposure, will powerfully facilitate the identification of biological and molecular disturbances that are relevant to human depression.

Methods: We addressed three critical issues of antidepressant effects: (1) what is the extent of chronic antidepressant drug exposure effect on the brain transcriptome in mice (cingular and amygdala) compared to the effects of UCMS; (2) What is the extent of peripheral transcriptome changes in blood of mice exposed to UCMS and to UCMS plus fluoxetine? And, (3) how do peripheral blood changes compare those observed in the brain?

Results: We show that antidepressants (SSRI and CRFR1 antagonism) affect much larger gene numbers than UCMS, consistent with their pervasive effects on neurotransmitter systems, and that UCMS constraints the overall plasticity of the brain, resulting in different and fewer AD effects, compared to the effect of drugs in control mice. Importantly, if peripheral UCMS and antidepressant-induced transcriptome changes were to be conserved between the brain and blood, they would identify genes with both peripheral biomarker value and as indirect indicators of central mechanisms.

Conclusions: Results will be critical in supporting the analysis of more complex changes observed in human patients.

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608.-632. 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.