Neuropsychopharmacology (2012) 38, S198–S313

Poster Session II
Tuesday, December 04, 2012

T2. Schizophrenic and Bipolar Tobacco Smoker/nonsmoker Sex, Dopamine D2 Receptor Taq1A and OPRM1 A118G Genotype Differences

Edward F. Domino*, Mika Hirasawa-Fujita, Michael Bly, Vicki Ellingrod, Gregory Dalack

University of Michigan, Ann Abor, Michigan

Background: Why the mentally ill smoke tobacco more than normal persons is unknown. The objectof the present study was to determine the OPRM1 A118G (rs1799971), dopamine D2receptor (DRD2) Taq1A (rs1800497) genotype, and sex differences of schizophrenicand bipolar smokers vs nonsmokers.
Methods: A total of 177 schizophrenic and 110 bipolar patients were recruited andgenotyped. They were classified into three groups: current smoker, formersmoker, and never smoker by tobacco smoking status self reports. The number ofcigarettes smoked per day was used to estimate the degree of tobacco smokingreinforcement. Genomic DNA was extracted from whole blood with the GentraPuregene Blood kit (QIAGEN). The Polymerase Chain Reactions (PCR) wereperformed using One Taq 2X Master Mix with standard buffer.
Results: Tobacco smoking was more prevalent in male than in female schizophrenics, but equal inbipolar males and females. Surprisingly, female schizophrenic patients smoked more cigarettes per day than the males ($p < 0.01$). The schizophrenic OPRM1 *Gcarriers smoked more than the AA alleles ($p < 0.05$). Overall, DRD2 Taq1A genotypedifferences had no effect on the number of cigarettes smoked per day. Thepresence of the A1 (A) allele of DRD2 was not associated with greaterprevalence of tobacco smoking. However, homozygous A2 (GG) allele carriers smoked more than patients with DRD2 AA/AG or GG genotypes.
Conclusions: This study indicates sex, DRD2 Taq1A and OPRM1 genotype differences among tobaccosmoking and nonsmoking schizophrenic and bipolar patients. Female schizophrenicOPRM1 *G and patients with DRD2 A2 (GG) alleles smoked more than the others.
Keywords: Genotying, mentally ill, tobacco smoking
Disclosure: E. Domino, Nothing to Disclose; M. Hirasawa-Fujita, Nothing to Disclose; M. Bly, Nothing to Disclose; V. Ellingrod, Nothing to Disclose; G. Dalack, Nothing to Disclose.

T3. Trauma and Post Traumatic Stress Disorder in an American Indian Community: Heritability, Electrophysiological Findings, and Comorbidity with Other Psychiatric Disorders

Cindy L. Ehlers*, Ian Gizer, David Gilder, Rachel Yehuda

The Scripps Research Institute, La Jolla, California

Background: American Indians appear to experience a higher rate of traumatic events that what has been reported in general population surveys. American Indians also suffer higher alcohol related death rates than any other U.S. ethnic group in the U.S. population. Therefore efforts to delineate factors which may uniquely contribute to increased likelihood of trauma, post traumatic stress disorder (PTSD), and substance use disorders (SUD) over the lifetime in American Indians are important because of the high burden of morbidity and mortality that they pose to American Indian communities. Therefore, the aims of the present study were:1) to document the range of traumatic events reported in an American Indian community; 2) to study the relationship of traumatic events to PTSD; 3) to estimate the heritability of PTSD and trauma exposure; and 4) to study electrophysiological concomitants of PTSD 5) to determine the comorbidity of trauma and PTSD with substance dependence, affective disorder, and conduct disorder.
Methods: Participants were 309 American Indians recruited from reservations who were assessed with the semi-structured assessment for the genetics of alcoholism (SSAGA), and the *stressful-life-events scale*. Electroencephalogram (EEG) spectra and visual event-related potentials (ERPs) to happy, sad, and neutral faces were also recorded from 146 of the participants.
Results: Of the 309 participants, equivalent numbers of men and women (94%) reported experiencing at least 1 of 7 types of traumas. All trauma types were significantly associated with PTSD except natural disaster with loss. A larger proportion of women received a PTSD diagnosis (38%) than men (29%). Multiple trauma and sexual abuse were most highly associated with PTSD. Having experienced assaultive trauma and having PTSD symptoms were both found to be moderately heritable (30-50%). An electrophysiological signature for PTSD was found that included increases in high-frequency gamma activity in frontal leads, higher N1 amplitudes to sad stimuli in frontotemporal leads, and longer latency P3 components to happy stimuli in midline, central, and right frontal leads. Logistic regression revealed that in a larger model that age and gender were not significantly associated with PTSD, but having an anxiety and/or affective disorder and having a substance dependent diagnosis was significantly correlated with having a diagnosis of PTSD.
Conclusions: These studies suggest that trauma is highly prevalent this American Indian community and that it is associated with PTSD electrophysiological findings, affective and anxiety disorders and substance dependence. These findings further suggest that substance abuse treatment programs for American Indians may benefit from addressing issues related to trauma, PTSD and its associated symptomatology.
Keywords: Native American, substance dependence, PTSD, heritability
Disclosure: C. Ehlers, Nothing to Disclose; I. Gizer, Nothing to Disclose; D. Gilder, Nothing to Disclose; R. Yehuda, Nothing to Disclose.

T4. MicroRNA-137 Expression in Schizophrenia and Bipolar Disorder

Marquis P. Vawter*, Ilaria Guella, Brandi Rollins, Theo Van Erp, Federica Torri, Pedro A. Sequeira, William E. Bunney, Steven Potkin, Fabio Macciardi

University of California, Irvine, California

Background: MicroRNAs (miRNAs) are small non-coding RNAs that act as potent regulators of gene expression. In a recent GWAS the rs1625579 SNP, located downstream of miR-137, was reported as the strongest new association with schizophrenia (1). Previous to the GWAS finding, independent imaging-genetic studies found miR-137 to be 1 of 3 miRNAs with target genes significantly enriched for association with prefrontal cortex (DLPFC) inefficiency in SZ (2). Strikingly, this miRNA has been implicated in regulating both adult neurogenesis and neuronal maturation.
Methods: We investigated the miR-137 expression levels in the DLPFC of postmortem brain tissue from 2 independent cohorts: 1) 27 subjects (10 controls (CTR), 8 schizophrenia (SZ), and 9 bipolar disorder (BD)) collected at the UCI Brain Bank; and 2) 99 subjects (33 CTR, 35 SZ, 31 BD) obtained from the Stanley Medical Research Institute (SMRI). The rs1625579 genotypes of 106 combined samples wereinvestigated for an association with miR-137 expression.
Results: Within the UCI cohort, we observed a statistically significant difference in DLPFC miR-137 expression across the 3 groups ($p < 0.05$), with the BD having a higher expression (2.01 fold increase) and the SZ a lower expression (0.69 fold decrease)

compared to the control group. We were not able to replicate these results in the SMRI collection, but in both cohorts there was a slight reduction in miRNA-137 expression in SZ. Comparing the rs1625579 genotypes across all pooled groups, miR-137 expression in DLPFC was decreased 1.18 fold in the homozygous TT subjects compared to TG/GG subjects in a joint analysis of the 2 cohorts, although this difference did not achieve statistical significance ($p = 0.19$). When controls were analyzed separately in the joint analysis, the miR-137 expression was 1.41 fold lower in TT subjects compared to TG ($p = 0.036$). We found regional expression of mir-137 to be inversely correlated in the amygdala and DLPFC ($r = -0.86$, $p = 0.003$) for a subgroup of nine subjects that were studied in 11 brain regions. We are reporting brain activation results for DLPFC at this meeting (van Erp TG et al., abstract submitted) as a function of miR-137 genotypes.

Conclusions: We have thus far investigated expression in the DLPFC where our results suggest a possible association between the T risk allele of rs1625579 and decreased miR-137 expression in controls. We will analyze expression of candidate target genes for miR-137 and report those results. Of interest is a negative correlation of miR-137 expression between DLPFC and amygdala in the same subjects which if confirmed in a larger sample could have ramifications for regional expression pattern differences that are associated with neuronal maturation and neurogenesis.

References: 1. Potkin SG, et al. (2010). Identifying gene regulatory networks in schizophrenia. Neuroimage. Nov 15;53(3):839-47. Epub 2010 Jun 22. 2. Ripke S., et al. (2011). Genome-wide association study identifies five new schizophrenia loci. Nat Genet. Sep 18;43 (10):969-76.

Keywords: microRNA mir-137 GWAS gene expression

Disclosure: M. Vawter, Nothing to Disclose; I. Guella, Nothing to Disclose; B. Rollins, Nothing to Disclose; T. Van Erp, Nothing to Disclose; F. Torri, Nothing to Disclose; P. Sequeira, Nothing to Disclose; W. Bunney, Nothing to Disclose; S. Potkin, **Part 1:** Bristol-Myers Squibb, Eisai, Inc., Eli Lilly, Forest Laboratories, Genentech, Janssen Pharmaceutical, Lundbeck, Merck, Novartis, Organon, Pfizer, Roche, Sunovion, Takeda Pharmaceutical, Vanda Pharmaceutical, **Part 2:** Lundbeck, Merck, Novartis, Sunovion, **Part 3:** Lundbeck, Merck, Novartis, Sunovion, **Part 4:** Amgen, Baxter, Bristol-Myers Squibb, Cephalon, Inc., Eli Lilly, Forest Laboratories, Genentech; F. Macciardi, Nothing to Disclose.

T5. Gene x Withdrawal Effects on Responsiveness to Cocaine Stimuli in Cocaine Addiction

Scott J. Moeller*, Muhammad Parvaz, Elena Shumay, Nicasia Beebe-Wang, Nora D. Volkow, Rita Goldstein

Brookhaven National Laboratory, Upton, New York

Background: Functional polymorphisms in dopamine-related genes modulate dopamine neurotransmission, reward-related responsiveness, and behavior. For example, compared with individuals with two 10R alleles of the dopamine transporter gene (*DAT1*), individuals with a 9R allele show increased responsiveness to reward (higher ventral striatal response to money, elevated smoking-induced dopamine release). Here we examined the impact of the polymorphism in the *DAT1* gene on responsiveness to cocaine pictures in individuals with cocaine use disorder (CUD). Our novel approach included multi-modal dependent variables (psychophysiological scalp recordings, self-report, behavior) and consideration of a deprivation state (acute cocaine withdrawal).

Methods: 73 CUD (64% African American, 33% Caucasian, 3% Other) (35 of whom tested positive for cocaine in urine, indicating use within 72 hours and reflecting a state of acute cocaine withdrawal) and 47 healthy controls (60% African American, 36% Caucasian, 4% Other) underwent the following study procedures: (A) *DAT1* genotyping [the VNTR polymorphism in the 3′ untranslated region of the *SLC6A3* gene (3′-UTR VNTR), using whole blood extracted DNA samples]; (B) scalp-recorded event-related potentials (specifically, the slow wave, which appears 400-2000 milliseconds after stimulus onset and is thought to be a bottom-up measure of stimulus salience) during passive viewing of pleasant, unpleasant, neutral, and cocaine images; (C) rating of these same images on pleasantness and arousal; and (D) completion of two previously validated choice tasks (one with explicit task contingencies and one with more implicit task contingencies) that assess choice (behavior) for viewing these same images. To ensure a sufficient number of subjects per cell, and consistent with previous research, analyses primarily compared homozygous carriers of the 10R-allele (10R/10R genotype ($N = 70$) with individuals carrying a 9R-allele (encompassing 9R/10R and 9R/9R genotypes ($N = 50$). Specifically, five separate 3 (cocaine urine status: positive, negative, control) × 2 (*DAT1*: 10R/10R genotype, 9R-allele carriers) analyses of variance (ANOVAs) were conducted on the following dependent measures: slow wave, self-report ratings of pleasantness and arousal, and implicit and explicit choice tasks (all subjects with available data were used for each analysis). The primary contrast of interest for these dependent measures was cocaine images > pleasant images, thus juxtaposing two salient picture categories in CUD.

Results: Across all five variables, both CUD groups showed greater responsiveness to the cocaine > pleasant image contrast than controls as expected ($p < 0.05$, planned comparisons), while group main effects of *DAT1* were not significant ($p > 0.2$). Importantly, for the slow wave, the urine status × *DAT1* interaction was significant [$F(2,105) = 4.27$, $p < 0.05$], explained by a urine group difference (positive > negative) in the 9R-allele subjects but not in the 10R/10R subjects. For the other four variables, although the omnibus urine status × *DAT1* interactions were not significant, similar urine group differences (positive > negative) emerged only in the 9R-allele subjects (reaching significance for pleasantness ratings and implicit choice, $p < 0.05$). These core results were strengthened by supplemental analyses: (A) further supporting the idea that urine status effects reflected withdrawal/deprivation, only in the 9R-allele carriers did the slow wave correlate with more cocaine craving (as measured by a well-validated self-report questionnaire) (9R-allele: $r = 0.62$, $p < 0.01$; 10R/10R: $r = 0.06$, $p > 0.6$; correlation difference: $t = 3.62$, $p < 0.001$) and fewer days of current cocaine abstinence (9R-allele: Spearman $r = -0.43$, $p < 0.05$; 10R/10R: Spearman $r = 0.07$, $p > 0.6$; correlation difference: $t = 2.13$, $p < 0.05$); (B) urine status × *DAT1* interactions were not significant when analyzing related, but non-drug-salient tasks (of attention and inhibitory control: attention network task and color word Stroop task, respectively, all $p > 0.1$); and (C) demographic and other relevant clinical variables that differed between the groups did not attenuate these effects when covaried (with analysis of covariance or partial correlation as appropriate).

Conclusions: Taken together, CUD carrying the *DAT1* 9R allele exhibited higher electrocortical responsiveness to cocaine-related stimuli – but only if these individuals were in acute cocaine withdrawal as indicated by positive cocaine urine screens. These results extend previous research that has revealed increased reward sensitivity in 9R-allele carriers, here offering the intriguing and novel suggestion that such sensitivity might be context-dependent (e.g., when in a state of current deprivation and/or when exposed to salient cues). Because such modulation by urine status was ostensibly due to the effects of short-term abstinence and/or increased craving, future studies could test the hypothesis that addicted individuals carrying the 9R allele are particularly susceptible to cue-induced craving during early detoxification. Such individuals could then be targeted for additional therapeutic intervention to help regulate reactivity to drug-associated stimuli during this critical period of treatment.

Keywords: DAT1; cocaine addiction; event-related potentials; cocaine choice behavior; withdrawal

Disclosure: S. Moeller, Nothing to Disclose; M. Parvaz, Nothing to Disclose; E. Shumay, Nothing to Disclose; N. Beebe-Wang, Nothing to Disclose; N. Volkow, Nothing to Disclose; R. Goldstein, Nothing to Disclose.

T6. Allele-specific DNA deMethylation in FKBP5: A Molecular Mediator of Gene x Environment Interactions with Childhood Trauma

Torsten Klengel*, Divya Mehta, Christoph Anacker, Jens C. Pruessner, Carmine M. Pariante, Thaddeus WW. Pace, Kristina B. Mercer, Helen S. Mayberg, Bekh Bradley, Charles Nemeroff, Florian Holsboer, Christine M. Heim, Kerry J. Ressler, Theo Rein, Elisabeth Binder

Max Planck Institute of Psychiatry, Munich, Germany

Background: For most psychiatric diseases neither a genetic disposition nor environmental factors on its own are sufficient to elicit a specific disorder. Rather, genetic variation and environmental exposure interact to shape the development and function of the human brain and ultimately moderate the risk to suffer from psychiatric disorders. Here, we delineate an epigenetic mechanism for the gene x environment (GxE) interaction of the gene with childhood abuse on the development of post-traumatic stress disorder (PTSD) in adulthood.

Methods: Data from this study were collected as part of the Grady Trauma Project and replication was performed in data from the Conte Center Study for the Psychobiology of Early-Life Trauma (Emory University, Atlanta, GA, USA). Individuals were assessed using different measures for PTSD and childhood abuse. For genotyping and pyrosequencing, DNA was extracted from peripheral blood. Methylation analysis was performed by pyrosequencing of bisulfite treated genomic DNA. The functional impact of differential methylation was analyzed using a CpG free luciferase reporter construct and an GR sensitivity assay. In addition, we used a multipotent hippocampal progenitor cell line to assess the methylation status of FKBP5in human neuronal cells in response to dexamethasone stimulation.

Results: FKBP5 rs1360780 interact with child abuse exposure (CTQ) on the development of current PTSD symptoms (mPSS) in adulthood ($F_{1963,2} = 4.40$, $P = 0.012$). The risk to suffer from lifetime PTSD (CAPS) is significantly increased by exposure to early trauma in *FKBP5* risk allele carriers ($\chi^2 = 28.6$, df = 2, $P < 0.001$), but not in carriers of the protective genotype ($\chi^2 = 2.02$, df = 2, $P = 0.36$). Pyrosequencing of bisulfite treated DNA of highly traumatized individuals and controls revealed a significant demethylation of CpGs around glucocorticoid responsive elements (GREs) of *FKBP5* in abused individuals. We found a significant interaction of *FKBP5* genotype and childhood abuse on DNA methylation level in 3 CpGs in intron 7 ($F_{73,1} = 31.01$, $P_{corr} < 0.001$). When correlating level of child abuse using the Childhood Trauma Questionnaire (CTQ) with the methylation of intron 7, significant differences in the correlation coefficients were observed between the risk allele carriers and carriers of the protective allele ($R = -0.646$, $P < 0.001$ and $R = 0.414$, $P = 0.078$, Fisher Z-score of $-4{,}23$, P-value $= 7.0 \times 10^{-5}$). This emphasizes the effects of early trauma severity on *FKBP5* demethylation in risk allele carriers, but not in carriers of the protective allele. Replication in an independent cohort from the Conte Center Study confirm these findings. Employing a CpG-free reporter construct, we demonstrate that changes in DNA methylation in intron 7 alter glucocorticoid responsiveness of *FKBP5in vitro*. An *ex-vivo* GR sensitivity assay demonstrate that intron 7 DNA methylation alters the ultra-short feedback loop between GR and *FKBP5* and thus GR sensitivity with reduced methylation in intron 7 associated with higher induction of FKBP5 by GR, representing an enhancement of the ultra-short feedback loop leading to increased GR resistance. In a multipotent human hippocampal progenitor cell line we show that *FKBP5* demethylation is initiated by GR-activation with dexamethasone which led to a highly significant DNA demethylation in CpGs in intron 7 similar to the CpGs in intron 7 affected by early trauma in *FKBP5* risk allele carriers (average of 17.1% demethylation in these 3 CGs, $P < 0.001$). We currently extend these results comparing DNA methylation changes in dexamethasone treated hippocampal progenitor cells with trauma exposed individuals on Illumina's 450k methylation bead chip. Preliminary data suggest a strong allele-dependent overlap between methylation in neuronal cells and childhood abused individuals.

Conclusions: *FKBP5*, an important regulator of the stress hormone system, increase the risk of developing PTSD by allele-specific, childhood trauma-dependent demethylation of CpGs in functional GREs of *FKBP5*. For the first time, we delineate a molecular mechanism by which environmental impact in early life is encoded in epigenetic modifications and moderated by genetic predisposition influencing the development of psychiatric symptoms in later life. Our findings might be of particular relevance for the developing organism since the effects on DNA methylation seemed to be restricted to exposure to childhood trauma and were not influenced by traumatic experiences in adulthood, suggesting a possible sensitive period in early development for these epigenetic effects.

Keywords: epigenetics, post traumatic stress disorder, gene-environment interaction, FKBP5, childhood abuse

Disclosure: T. Klengel, Nothing to Disclose; D. Mehta, Nothing to Disclose; C. Anacker, Nothing to Disclose; J. Pruessner, Nothing to Disclose; C. Pariante, Nothing to Disclose; T. Pace, Nothing to Disclose; K. Mercer, Nothing to Disclose; H. Mayberg, **Part 1:** Dr. Mayberg has a consulting agreement with St Jude Medical Inc., which has licensed her intellectual property to develop SCC DBS for the treatment of severe depression; B. Bradley, Nothing to Disclose; C. Nemeroff, **Part 1:** Dr. Nemeroff has grant support from NIMH and the Agency for Healthcare Research and Quality. He consults to Xhale, Takeda and Allergen. He is stockholder in CeNeRx BioPharma, NovaDel Pharma, Inc., PharmaNeuroBoost, Revaax Pharma and Xhale and has other financial interests in CeNeRx BioPharma and PharmaNeuroBoost. He is on the scientific advisory boards of the American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma, National Alliance for Research on Schizophrenia and Depression (NARSAD), NovaDel Pharma, Inc., PharmaNeuroBoost and the Anxiety and Depression Association of America (ADAA) and on the Board of Directors for AFSP and NovaDel Pharma, Inc. Dr. Nemeroff holds patents for: Method and devices for transdermal delivery of lithium (US 6,375,990B1) and method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by *ex vivo* assay (US 7,148,027B2); F. Holsboer, **Part 1:** Dr. Holsboer is founder and share holder of Affectis Pharmaceuticals and Holsboer Maschmeyer NeuroChemie GmbH, Dr. Holsboer is also inventor of: Means and methods for diagnosing predisposition for treatment emergent suicidal ideation (TESI). European application number: 08016477.5 International application number: PCT/EP2009/061575, Polymorphisms in ABCB1 associated with a lack of clinical response to medicaments. International application number: PCT/EP2005/005194 and, FKBP5: a novel target for antidepressant therapy. International publication number: WO 2005/054500; C. Heim, Nothing to Disclose; K. Ressler, **Part 1:** Within the last 3 years, Dr Ressler has received research funding support from Lundbeck and he has an unrelated role as co-founder of Extinction Pharmaceuticals for development of N-methyl-D-aspartate-based therapeutics; T. Rein, **Part 1:** Dr Rein is inventor of: FKBP5: a novel target for antidepressant therapy. International publication number: WO 2005/054500; E. Binder, **Part 1:** Dr. Binder receives grant support from PharmaNeuroBoost, Dr. Binder is inventor of: Means and methods for diagnosing predisposition for treatment emergent suicidal ideation (TESI). European application number: 08016477.5 International application number: PCT/EP2009/061575, Polymorphisms in ABCB1 associated with a lack of clinical response to medicaments. International application number: PCT/EP2005/005194 and FKBP5: a novel target for antidepressant therapy. International publication number: WO 2005/054500.

T7. APOE ε4, an Alzheimer's Disease Susceptibility Allele, Predicts Relapse among Older Treatment-seeking Smokers

Rebecca L. Ashare*, Jason Karlawish, E. Paul Wileyto, Angela Pinto, Caryn Lerman

University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

Background: Possessing an ε4 allele of the *APOE* gene, advanced age, and persistent smoking are known risk factors for Alzheimer's disease and cognitive decline. Deficits in cognitive function also increase risk for failed smoking cessation attempts. This study examined whether smokers who carry the ε4 allele have more difficulty quitting smoking.
Methods: Data from 917 adult treatment-seeking smokers of European ancestry were pooled across three randomized clinical trials of smoking cessation treatment conducted between 1999 and 2008. Smoking relapse outcomes were compared between carriers with at least one ε4 allele (n = 252) versus noncarriers (n = 665), and the potential modifying effect of age was tested. The primary outcome was biochemically verified 7-day point-prevalence abstinence rate, measured at the end of treatment and 6-month follow-up. A secondary outcome was time to 7-day failure censored at six months.
Results: The genotype by age interaction was significant for abstinence rate ($p = 0.04$) and time to failure ($p = 0.03$). Among smokers over age 60, ε4 carriers were significantly less likely to quit (OR = 0.27, 95% CI = 0.092-0.798, $p = 0.018$) and relapsed more quickly (HR = 3.38, 95% CI = 1.62-7.05, $p = 0.001$) compared to ε4 noncarriers. The genotype association with relapse outcomes was non-significant among younger smokers.
Conclusions: Among healthy older smokers, the *APOE* ε4 allele reduces the likelihood of quitting smoking and time to relapse. An increased understanding of the underlying pathophysiological mechanisms of this association could potentially facilitate the development of targeted therapies for smokers with increased risk for cognitive decline.
Keywords: smoking; smoking cessation; nicotine; cognition; APOE
Disclosure: R. Ashare, Nothing to Disclose; J. Karlawish, Nothing to Disclose; E. Wileyto, **Part 1:** Dr. Wileyto has served as a consultant for Pfizer; A. Pinto, Nothing to Disclose; C. Lerman, **Part 1:** Dr. Lerman has served as a consultant and/or has received research funding from GlaxoSmithKline, AstraZeneca, Novartis, and Pfizer. The current study was not supported by industry funds.

T8. The Catechol-O-methyltransferase (COMT) Val158Met Polymorphism Interacts with Childhood Trauma to Influence Aggression and Impulsivity among Treatment-seeking Alcohol Dependent Individuals

Melanie Schwandt*, Markus Heilig, Daniel W. Hommer, David T. George, Colin A. Hodgkinson, Pei-Hong Shen, David Goldman, Vijay Ramchandani

National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland

Background: Both genetic and environmental factors are believed to play a role in aggressive and impulsive behavior. The importance of catecholamines (e.g., norepinephrine and dopamine) in the regulation of impulsive behavior is well understood, but only recently have catecholamines been implicated in the regulation of aggressive behavior. Variation at the COMT Val158Met locus has been associated with aggressive behavior, however the findings are largely based on studies in schizophrenics. In this study, we investigated potential effects of variation at the COMT Val158Met locus and of childhood trauma on aggressive and impulsive tendencies among individuals with alcohol dependence.
Methods: Data were obtained from 179 alcohol dependent subjects (124 males, 55 females) admitted for inpatient treatment at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD. All individuals were diagnosed with alcohol dependence according to the Structured Clinical Interview for DSM-IV (SCID), and alcohol dependence severity was assessed using the Alcohol Dependence Scale (ADS). COMT Val158Met genotypes were determined using the Illumina® OmniExpress BeadChip (Illumina, Inc., San Diego, CA). Childhood trauma was assessed using the overall severity score from the Childhood Trauma Questionnaire (CTQ). Aggression was assessed using the Buss Perry Aggression Questionnaire (BPAQ), while impulsivity was assessed using both the Barratt Impulsiveness Scale (BIS) and the Delay Discounting task. In addition the personality subfacets of Impulsiveness and Anger/Hostility, measured by the NEO Five Factor Personality Assessment, were assessed. Data were analyzed using analysis of covariance (ANCOVA).
Results: Of the 179 subjects, 37 (20.6%) were genotyped as Met/Met, 89 (49.7%) as Val/Met, and 53 (29.6%) as Val/Val. There was no difference in CTQ total score between the genotype groups. Main effects of genotype were found for the total aggression score ($F = 4.93$, $p = 0.008$), and for the anger ($F = 5.77$, $p = 0.004$) and hostility ($F = 4.08$, $p = 0.019$) factors from the BPAQ, with Met/Met subjects scoring higher on these measures. However, significant interactions between genotype and childhood trauma scores were found for total aggression ($F = 3.07$, $p = 0.049$) and anger ($F = 3.57$, $p = 0.031$). Val/Met and Val/Val subjects showed increasing levels of aggression and anger scores with increasing levels of childhood trauma, while the Met/Met subject did not. Interactions between genotype and childhood trauma scores were also found for BIS total score ($F = 4.93$, $p = 0.008$), the second-order factors of Attentional Impulsiveness ($F = 5.10$, $p = 0.007$) and Non-Planning Impulsiveness ($F = 3.41$, $p = 0.035$) from the BIS, and for the Delay Discounting task ($F = 3.51$, $p = 0.033$). Similar to the results for aggression, Val/Met and Val/Val subjects showed significant positive associations between childhood trauma and measures of impulsivity, while Met/Met subjects did not. The Anger/Hostility and Impulsiveness personality subfacets from the NEO both showed positive associations with CTQ total score but no main or interactive genotype effects.
Conclusions: Our findings provide further evidence for the role of catecholamines in regulating aggressive and impulsive behavior. Variation in the COMT gene that influences enzymatic activity, and thus alters the degradation of dopamine and norepinephrine, was found to moderate the effects of childhood trauma on both aggressive and impulsive measures, in particular anger, attentional impulsiveness, and non-planning impulsiveness. The lack of genotype effects on more trait-like measures of anger and impulsiveness from the NEO suggests that catecholamines are involved in the regulation of angry and impulsive emotional states, rather than chronic or stable tendencies.
Keywords: catecholamines, aggression, impulsivity, alcohol dependence, childhood trauma
Disclosure: M. Schwandt, Nothing to Disclose; M. Heilig, Nothing to Disclose; D. Hommer, Nothing to Disclose; D. George, Nothing to Disclose; C. Hodgkinson, Nothing to Disclose; P. Shen, Nothing to Disclose; D. Goldman, Nothing to Disclose; V. Ramchandani, Nothing to Disclose.

T9. eQTL Regulation by NATs in Alzheimer's Disease

Amanda Myers*, Manuel Ramirez

University of Miami, Miller School of Medicine, Miami, Florida

Background: We have found that ~10% of the human brain transcriptome is under genetic control. While these expression quantitative trait loci (eQTLs) exist both in control samples and LOAD samples, for some of them there is a difference in the SNP-transcript relationship in LOAD. Our hypothesis is that one process by which eQTL mis-regulation could occur in LOAD is through the influence of natural antisense transcripts (NATs). NATs are non-protein-coding, but fully processed RNAs that are transcribed from the opposite strand of the protein-coding sense

transcript. NATs can regulate the expression of their corresponding protein-coding sense transcripts, with beta-secretase regulation being a prime example of relevance to LOAD. We have examined the top 100 eQTL hits from our screen of ~1200 human samples to determine whether **1.*** A NAT exists for the eQTL of interest, **2.*** The mapped NAT is differentially expressed within our series and **3.*** The NAT appears to regulate the eQTL of interest.
Methods: The following criteria were used to pick putative NATs: 1. NATs had to be within the EST database, 2. NATs had to be novel, 3. NATs had to be on the antisense strand and finally, 4. NATs had to be spliced. RT-PCR was performed and differential expression (DE) of each NAT was assessed comparing cases and controls. Initial screening was performed in 6 cases and 5 controls. DE was assessed using standard delta delta CT methods. Further screening was performed using 376 controls and 515 cases. To confirm causation, we will use shRNA to knockdown the NAT of interest and determine the effect on the corresponding eQTL transcript and protein levels.
Results: We found that ~25% of screened eQTL had at least one corresponding NAT. Of those tested in our initial screens, one NAT showed a significant difference in expression between cases and controls, as well as a significant difference in cases versus controls expression when eQTL genotype group was considered.
Conclusions: We have mapped transcripts which are under genomic control and where there is an alteration in eQTL profiles LOAD. We now show that NAT transcripts could play a role in this mis-regulation.
Keywords: expression quantiative trait locus; natural antisense transcript; transcriptome; Alzheimer's disease
Disclosure: A. Myers, Nothing to Disclose; M. Ramirez, Nothing to Disclose.

T10. Association of PACAP and PACAPR1 Gene Variants with Unipolar Depression and Panic Disorder

Angelika Erhardt*, Susanne Lucae, Marcus Ising, Florian Holsboer, Elisabeth Binder

Max Planck Institute for Psychiatry Munich, Germany

Background: Depressive and anxiety disorders are the most prevalent psychiatric conditions in the general population with the life-time prevalence up to 20% respectively. Family and twin studies have clearly shown that genetic factors are implicated in the pathophysiology of depression and anxiety disorders with the estimated heritability of 30-50%. Environmental factors, such as stressful life events and other stress-related conditions, increase the risk for the development of depression and pathological anxiety. Therefore, candidate genes involved in the functioning of the endogenous stress system, called Hypothalamus-Pituitary-Adrenocortical (HPA) – System are of interest for the development of anxiety and depression. Pituitary adenylate cyclase-activating polypeptide (PACAP or *ADCYAP1*) und its receptor one (PAC1 or *ADCYAP1R1*) are upregulated following chronic stress in brain areas implicated in emotional control of behaviour and deficiency of PACAP and PAC1 influence anxiety- and depression like behaviour in mice. In line with this, recently, an association of an intronic variant (rs2267735) in a putative oestrogen response element in the PAC1 gene with posttraumatic stress disorder in females have been found (Ressler 2011).
Methods: In order to elucidate the genetic contribution of PACAP and PAC1 to depression and anxiety disorders, we performed a case-control association analysis of SNPs in the genes PACAP and PAC1 in two samples with unipolar depression (MDE) patients (Combined: n = 1557 cases, n = 1403 controls) and one sample with panic disorder (PD) patients (n = 244 cases, n = 542 controls). Additionally, we analysed variants in the PACAP and PAC1 genes for association with parameters in the Dex-CRH-Test as an indicators of alterations in the HPA-system.
Results: In the case-control analysis of single SNPs in the PACAP gene nominal associations with depression were detected. The haplotype analysis showed significant values for three haplotypes located mainly in the promoter region of the gene. In the PAC1 gene, 6 SNPs were highly associated with depression. These SNPs were located in the intron 14 and the downstream region of the gene. No associations with any SNPs in the PACAP or PAC1 genes were detected for PD. Interestingly, in the analysis of parameters in the Dex-CRH-Test, SNPs in the PAC1 gene were significantly associated with the Area under the curve of ACTH (Aauc) in the PD group. The same set of SNPs was nominally associated with the area under the curve of Cortisol (Cauc) in PD and Aauc/Cauc in the depressed group. The SNP previously associated in the PTSD group (rs2267735) was nominally associated with Cauc in the depressed group. In contrast to the study in PTSD patients, no gender-specific effects could be found in the depressed and PD group.
Conclusions: In the present study, we first detected significant associations of SNPs in the PAC1 gene with depression. Additionally, interesting genetic effects have been found for parameters of the Dex-CRH-Test. In the PD group, the association of SNPs in the PAC1 gene with Dex-CRH-Test were prominent for the ACTH parameters suggesting a direct link to the effects of PAC1 in the pituitary.
Keywords: depression, anxiety, SNPs, PACAP, PAC1
Disclosure: A. Erhardt, Nothing to Disclose; S. Lucae, Nothing to Disclose; M. Ising, Nothing to Disclose; F. Holsboer, **Part 3:** Co-founder of the Holsboer-Maschmeyer-Neurochemie-GmbH; E. Binder, Nothing to Disclose.

T11. Genetic Variation in the PACAP-PAC1 Receptor (ADCYAP1R1) Gene is Associated with Increased Resting State Blood Flow in the Frontal and Limbic Regions Among Adolescent Females with High Childhood Emotional Neglect

Amy E. Ramage, Suman Baddam*, Megan N. Cullip, Rene L. Olvera, Douglas E. Williamson

University of Texas Health Science Center at San Antonio, San Antonio, Texas

Background: Pituitary adenylate cyclase-activating polypeptide (PACAP) is a 38 amino acid neuropeptide highly conserved in mammals that stimulates cAMP formation in anterior pituitary cells. PACAP and the specific type 1 receptor (PAC1) mRNA are expressed at highest levels in the hypothalamus and the limbic system (Vaudry et al. 2009). PACAP plays a central role in stress responses including the sympathoadrenomedullary and hypothalamic-pituitary-adrenal systems and is known to have neuroprotective and neurotropic actions (Hashimoto et al. 2011). In animal models, chronic variable stress increases the expression of PACAP and PAC1 in the brain regions associated with stress and anxiety like behavior. The PACAP and PAC1 knockout mice demonstrate increased depression and anxiety like behavior. (Hashimoto et al. 2009; Hammack et al. 2010). In human studies, Ressler et al. identified that the CC homozygote of the PAC1 receptor gene (ADCYAP1R1) rs2267735 SNP is associated with increased PTSD symptoms, particularly in females (Ressler et al. 2011). Similarly, we showed that CC homozygous female adolescents of ADCYAP1R1 rs2267735 SNP with higher levels of childhood stress had significantly higher levels of anxiety and depressive symptoms (Baddam et al., 2011). Building on our prior research, here, we explored the association between the CC homozygous PAC1 (ADCYAP1R1) rs2267735 SNP, gender, adolescent childhood stress and cerebral blood flow in fronto-limbic regions.
Methods: 245adolescents (Male: Female – 117:128, White: Hispanic: Others 138:93:14) aged 12-15 years (13.6 ± 0.97 years) were recruited from the greater San Antonio area and included in a prospective study examining genes, environment, and brain systems contributing to depression and alcohol use disorders. All subjects completed the Childhood Trauma Questionnaire (CTQ) and provided blood samples for DNA extraction at baseline. We genotyped the rs2267735 SNP located within the intron region NM_001118.3 of ADCYAP1R1 (PAC1 gene) and tested for C and G alleles from DNA isolated from blood using real time PCR. Pulsed arterial spin labeled MRI images were acquired to assess regional

cerebral blood flow (rCBF). Voxel-wise, whole brain multivariate regression analyses were computed to identify brain regions in which resting rCBF were associated with the PAC1 gene, childhood emotional neglect from the CTQ and/or gender.
Results: Allelefrequencies conformed to Hardy Weinberg Equilibrium with x 2 = 0.71, NS, with C allele frequency in the sample of 0.48. A significant three-way interaction ($F_{3,240} > 5.6$, $p < 0.001$) was found between gene-environment-gender attributable to CC homozygous adolescent females with increased childhood stress and increased cerebral blood flow in the bilateral putamen, the right middle frontal regions (BA 6, 46), right inferior frontal regions (BA 47), bilateral posterior cingulate cortex (BA 23, 30), right anterior cingulate gyrus (BA 24), right superior parietal lobe (BA 7), right primary motor cortex(BA 6,9), right middle temporal gyrus (BA 21), right insula (BA 13) and the left vermis of the cerebellum.
Conclusions: Interestingly, these results suggest a female specific gene x environment interaction in adolescence associated with the involvement of attentional, emotional and default mode network regions of the brain. Future research should focus on the translational and neuroendocrinal effects of the polymorphism and relate them to behavioral and imaging phenotypes.
Keywords: PACAP, ADCYAP1R1, rs2267735, adolescence, imaging
Disclosure: A. Ramage, Nothing to Disclose; S. Baddam, Nothing to Disclose; M. Cullip, Nothing to Disclose; R. Olvera; D. Williamson.

T12. Exome Sequence Analysis of Finnish Patients with Clozapine-induced Agranulocytosis

Arun K. Tiwari*, Anna C. Need, Clement C. Zai, Nabilah Chowdhury, Daniel J. Mueller (Müller), Anu Putkonen, Elia Repo-Tiihonen, Tero Hallikainen, A. Elif Anil Yağcỳoğlu, Jari Tiihonen, James L. Kennedy, Herbert Y. Meltzer

Centre for Addiction and Mental Health, Toronto, Ontario, Canada

Background: Clozapine is the prototypical atypical antipsychotic drug. Its primary indication is for treatment resistant schizophrenia and reduction of the risk for suicide. In spite of its efficacy, the use of clozapine is markedly curtailed by its side effects such as metabolic syndrome and agranulocytosis. While metabolic syndrome is more common than agranulocytosis, it is the latter which is the major reason that clinicians and patients are reluctant to consider the use of clozapine. Clozapine-induced agranulocytosis (CIA) occurs in about 0.8% of clozapine treated patients, generally within the first 18 weeks of treatment and is characterized by a decrease in absolute neutrophil count (ANC) below 500cells/mm^3. The aetiologic mechanism of CIA is unknown although several hypotheses have been proposed. These include nitrenium ion-mediated apoptosis, mitochondrial oxidative stress-induced apoptosis, or direct cytotoxicity against mesenchymal stromal cells in the bone marrow. In addition, an immune-mediated toxicity mechanism, based upon reoccurrence of agranulocytosis within several days of re-exposure to clozapine in patients who have had agranulocytosis, is considered to be a likely cause. Among the demographic risk factors for agranulocytosis are increased age and Asian or Finnish ancestry. Concordance of agranulocytosis has been reported in monozygotic twins and genetic polymorphisms, for example, in the major histocompatibility complex (HLA) genes [e.g. HLAB38 Lieberman et al., (1990) and HLA-DQB1 (6672G > C), Athanasiou et al., (2011)] have been associated with CIA. In this study we have utilized exome sequencing to comprehensively identify the genetic variations in the transcribed region of the genome in Finnish patients with and without CIA.
Methods: Schizophrenia or schizoaffective disorder patients (n = 50) diagnosed according to DSM-IV criteria were included in the study. Informed consent and approval by institutional ethics review board were obtained. Cases (n = 24) were diagnosed to be suffering from severe neutropenia (threatening agranulocytosis) based on the observation of a rapid decline in the absolute neutrophil count to less than 1500 cells/mm^3. Of these 24 patients, 13 developed a definite agranulocytosis (ANC $\leqslant$ 500 cells/mm^3) despite immediate discontinuation of clozapine. The enrichment of targeted regions (CCDS definition of exons and flanking introns, ~50Mb) was carried out using the Agilent SureSelect Human All Exon 50Mb Kit (Agilent Technologies, Santa Clara, CA) and the sequencing was carried out using the Illumina HiSeq 2000 platform (Illumina, Inc. San Diego, CA). Association between single nucleotide variants (SNVs), INDELs and CIA was tested using Fisher's exact test.
Results: A total of 143,258 SNVs and 14,778 INDELs were identified in the 50 individuals at $\geqslant$5x read depth. None of the SNVs or INDELs was significantly associated with CIA after Bonferroni correction ($p > 4.6 \times 10^{-7}$ after correction for 109,131 non-private SNVs and $p < 4.7 \times 10^{-6}$ after correction for 10,579 non-private INDELs). Among the top SNVs nominally associated with CIA, the odds ratio varied up to 19.3. However, the sequence coverage of some of these variants was low; therefore, these results should be interpreted with extra caution. We observed multiple signals in the *HLA-B/HLA-C* region. Carriers of the minor allele of these genetic variations in the *HLA-B/HLA-C* region were ~5-fold less likely to develop CIA when exposed to clozapine.
Conclusions: None of the SNVs achieved genome wide significance, suggesting that the genetic etiology is complex (e.g. locus or allelic heterogeneity, incomplete penetrance, epistasis), or that genetic variants that are not captured well by exome sequencing are responsible for CIA. In the light of previous findings, it is interesting to note that we observed nominal associations with multiple coding variants in the HLA-C gene. The HLA-C functions as a ligand for killer immunoglobulin receptors expressed on natural killer cells and can also present antigens to cytotoxic T-lymphocytes (CTL). Interestingly, replicated association of the common HLA-Cw7 antigen with CIA has been reported in non-Jewish German schizophrenia patients. The exact mechanism of how the HLA-C alleles might confer risk/protection for CIA is not clear. The relationship between HLA-C expression and the variations associated with CIA is not known. However, it is possible that in CIA, self-peptides are presented by HLA-C, leading to a CTL response which in turn leads to reduction in the number of neutrophils. Genetic variants affecting expression of HLA-C have been reported which may affect this self-antigen presentation, thereby increasing susceptibility to development of CIA. The HLA locus also exhibits long range linkage disequilibrium. Therefore, other HLA genes may contribute to CIA. In particular, the HLA-B gene, located ~85 kb upstream of HLA-C, has been associated with abacavir-induced hypersensitivity. It is important to note that these results did not reach study-wide significance, and the associations have not been validated with other genotyping methods, however, a fine scale genetic analysis of this HLA-B/C locus in a larger sample may be useful to confirm and better characterize the role of genetic variation in the HLA-B and –C genes in CIA susceptibility.
Keywords: Agranulocytosis, clozapine, exome sequencing, HLA-C, HLA-B
Disclosure: A. Tiwari, Nothing to Disclose; A. Need, Nothing to Disclose; C. Zai, Nothing to Disclose; N. Chowdhury, Nothing to Disclose; D. Mueller (Müller), Nothing to Disclose; A. Putkonen, Nothing to Disclose; E. Repo-Tiihonen, Nothing to Disclose; T. Hallikainen, Nothing to Disclose; A. Anil Ya∂cỳo∂lu, Nothing to Disclose; J. Tiihonen, **Part 1:** JT is a member of advisory board of AstraZeneca and Janssen-Cilag, and reports serving as a consultant to Lundbeck, Organon, Janssen-Cilag, Eli Lilly, AstraZeneca, F. Hoffman-La Roche, and Bristol-Myers Squibb. He has received fees for giving expert opinions to Bristol-Myers Squibb and GlaxoSmithKline, and lecture fees from Janssen-Cilag, Bristol Myers-Squibb, Eli Lilly, Pfizer, Lundbeck, GlaxoSmithKline, Novartis, and Astra Zeneca; J. Kennedy, **Part 1:** JLK has been a consultant to GSK, Sanofi-Aventis, and Dainippon-Sumitomo.; H. Meltzer, **Part 1:** HYM has received grants, or payment for lectures, or is or was a consultant to: Abbott Labs, ACADIA, Alkemes, Bristol Myers Squibb, DaiNippon Sumitomo, Eli Lilly, EnVivo, Janssen, Otsuka, Pfizer, Novartis, Roche, Sunovion, TEVA and BiolineRx. HYM is a shareholder of ACADIA, Glaxo Smith Kline and Suregene. HYM is a board member of Acadia, and is an advisor to Centerstone Research Institute.

T13. Oxytocin Genotype May Modulate Reactivity to the Environment in Borderline Personality Disorder

M. Mercedes Perez-Rodriguez*, Qiaoping Yuan, Zhifeng Zhou, Colin A. Hodgkinson, Laura Bevilacqua, Luis Ripoll, Marianne Goodman, Harold W. Koenigsberg, Pei-Hong Shen, David Goldman, Larry Siever, Antonia S. New

Mount Sinai School of Medicine, New York, New York

Background: It has been suggested that deficits in the attachment and affiliative system may underlie the impulsive aggressive reactions to perceived rejection and loss that are common in BPD, including suicidal and self-injurious behavior. Therefore, Oxytocin, a neuropeptide involved in attachment and affiliative behavior, may be altered in BPD. We aimed to examine associations between single nucleotide polymorphisms (SNPs) of the oxytocin (OXT) gene and BPD diagnosis and symptoms.
Methods: Subjects: 156 healthy controls (HCs), 181 patients with BPD, and 196 subjects with other personality disorders, assessed using the Structured Interview for DSM-IV PDs. A European American subsample was confirmed by European AIM scores >0.5 (HC = 82; BPD = 89; Other PDs = 92). 4 OXT SNPs (rs4813625, rs877172, rs2740210, and rs3761248) and 186 ancestry informative SNP markers were genotyped on a custom-designed Illumina array. We tested for an association between the SNPs and BPD diagnosis, and each specific BPD criterion. We also tested for an association between the SNPs and interpersonal functioning/social support measures. Corrections for multiple comparisons were done using the Bonferroni method.
Results: When we compared BPDs with HCs, we could not find any association of any of the explored SNPs with BPD diagnosis. When comparing BPD subjects with subjects with other personality disorders we found an association of BPD diagnosis with the rs2740210 SNP, which lost significance after correcting for multiple comparisons (Pearson Chi-square 6.79; df = 2; uncorrected $p = 0.033$; Bonferroni corrected $p = 0.396$). We could not find any significant association between the OXT SNPs and Interpersonal support evaluation list (ISEL), Experiences in close relationships inventory (ECRI), or Social Network Index (SNI) scores. We replicated a previously found (Siever LJ, personal communication) association between the rs877172 SNP and the 8th BPD criterion ("inappropriate, intense anger or difficulty controlling anger -e.g., frequent displays of temper, constant anger, recurrent physical fights-"). Those who tested positive for this criterion had lower rates of the A-containining genotypes (Fisher exact test uncorrected $p = 0.012$) than those who tested negative. We also found an association between the Interpersonal Reactivity Index Personal Distress subscale scores and OXT SNP rs4813625 genotypes. Post-hoc analyses revealed that mean IRI PD scores were significantly higher among r rs4813625 CG carriers than GG carriers (corrected $p = 0.018$). We also found an association between IRI Personal Distress subscale scores and OXT SNP rs877172 genotypes. Post-hoc analyses revealed that mean IRI PD scores were significantly higher among rs877172 AC carriers than AA carriers (corrected $p = 0.026$).
Conclusions: We found an association between OXT SNPs and irritable aggressive anger dysfunction and with the Interpersonal Reactivity Index Personal Distress subscale in personality disordered adults, suggesting the oxytocin system modulates reactivity to environment. This results need to be replicated in an independent sample.
Keywords: Borderline Personality Disorder; Oxytocin; Attachment; Impulsive aggression
Disclosure: M. Perez-Rodriguez, Nothing to Disclose; Q. Yuan, Nothing to Disclose; Z. Zhou, Nothing to Disclose; C. Hodgkinson, Nothing to Disclose; L. Bevilacqua, Nothing to Disclose; L. Ripoll, Nothing to Disclose; M. Goodman, Nothing to Disclose; H. Koenigsberg, Nothing to Disclose; P. Shen, Nothing to Disclose; D. Goldman, Nothing to Disclose; L. Siever, Nothing to Disclose; A. New, Nothing to Disclose.

T14. Genetic and Epigenetic Regulation of Catechol-O-Methyl-Transferase (COMT) are Associated with Impaired Fear Inhibition in Posttraumatic Stress Disorder

Seth D. Norrholm, Tanja Jovanovic, Alicia Smith, Elisabeth B. Binder, Torsten Klengel, Karen Conneely, Kristina B. Mercer, Jennifer Davis, Kimberly Kerley, Jennifer Winkler, Charles Gillespie, Bekh Bradley, Kerry J. Ressler*

Emory University School of Medicine, Atalnta

Background: The catechol-O-methyltransferase (COMT) enzyme is critical for the catabolic regulation of synaptic dopamine, resulting in altered cortical functioning. The *COMT* $Val^{158}Met$ polymorphism has been implicated in mental illness pathophysiology, with Met/Met homozygotes associated with increased susceptibility to posttraumatic stress disorder (PTSD). The primary objective of this work was to examine the intermediate phenotype of fear inhibition in PTSD stratified by *COMT* genotype (Met/Met homozygotes vs. Val allele carriers) and differential gene regulation via methylation status at CpG sites in the *COMT* promoter region and *COMT* mRNA expression in this population.
Methods: We examined the interaction of *COMT* genotype and PTSD diagnosis on fear-potentiated startle, *COMT* DNA methylation status, and *COMT* mRNA expression. The experimental setting consisted of medical and gynecological clinics of a major urban hospital in Atlanta, Georgia. Participants for the study included 270 unrelated participants with varying degrees of trauma exposure, of which 98 met criteria for PTSD, and 172 did not meet criteria for PTSD. Thirty participants had the *COMT* Met/Met genotype, and 240 were Val-allele carriers.
Results: The results revealed a significant interaction of genotype, PTSD diagnosis, and fear conditioning trial type. Focusing on the CS- (safety signal), we found main effects of genotype, and PTSD diagnosis, and an interaction of genotype and diagnosis, with highest fear to the safety signal in Met/Met carrier with PTSD. In addition, the Met/Met genotype associated with DNA methylation at 7 CpG sites, 4 of which were associated with higher fear-potentiated startle to the CS-. Finally, we found that lower *COMT* mRNA expression was associated with genotype and PTSD status.
Conclusions: These results suggest that multiple differential mechanisms for regulating COMT function – at the level of protein structure via the $Val^{158}Met$ genotype and at the level of gene regulation via differential methylation - are associated with impaired fear inhibition in PTSD.
Keywords: posttraumatic stress disorder, fear, genetics, catechol-o-methyltransferase, methylation
Disclosure: S. Norrholm, Nothing to Disclose; T. Jovanovic, Nothing to Disclose; A. Smith, Nothing to Disclose; E. Binder, **Part 1:** Dr. Binder has current grant support from PharmaNeuroBoost, **Part 4:** Dr. Binder has current grant support from PharmaNeuroBoost; T. Klengel, Nothing to Disclose; K. Conneely, Nothing to Disclose; K. Mercer, Nothing to Disclose; J. Davis, Nothing to Disclose; K. Kerley, Nothing to Disclose; J. Winkler, Nothing to Disclose; C. Gillespie, Nothing to Disclose; B. Bradley, Nothing to Disclose; K. Ressler, **Part 1:** Co-founder of Extinction Pharmaceuticals for development of N-methyl-D-aspartate– based therapeutics.

T15. Relationship of SYNE1 and Processing Speed with Interference Resolution in Bipolar Disorder

Scott A. Langenecker*, Aaron Vederman, Sebastian Zoellner, Masoud Kamali, Erika FH. Saunders, Melvin McInnis, Jon-Kar Zubieta, Margit Burmeister

University of Illinois at Chicago, Chicago, Illinois

Background: The present study investigated three genes shown to be involved in SCZ, BD, and/or MDD (Sklar et al., 2011; Williams et al., 2011): SYNE1, ANK3, and CACNA1C. Our previous work suggested that five cognitive factors would be high priority intermediate phenotypes for bipolar disorder (Langenecker et al.,

2010; Ryan, et al., in press). These include visual memory, fine motor function, verbal fluency and processing speed, processing speed with interference resolution, and conceptual reasoning and set shifting. We also reviewed the literature on bipolar disorder, on potential intermediate phenotypes including those studies with family members and at risk probands, which suggested auditory memory, neuroticism, and conscientiousness would also be a good candidate IPs for investigation (Bora, 2009; Mann-Wrobel et al., 2011; Pine, Ernst, and Leibenluft, 2010).
Methods: The Prechter Longitudinal Bipolar Study P5 (PLBS-P5) sample at the University of Michigan includes 586 adults aged 18-65 (Diagnostic Interview for Genetic Studies, DIGS; BD-I n = 307, BD-II n = 59, BD-NOS n = 33, BD Schizoaffective n = 13), also including a cohort of healthy comparison subjects (n = 159) with no history of mental illness. Some subjects initially screened as healthy control or bipolar disorder, had remitted MDD after DIGS (n = 13), and they are included within the mood disorders group. The mean for all mood disorder participants was 40.3 years of age and they had 15.2 years of education (M Hamilton Depression Rating Scale, HDRS = 8.9, SD = 6.3, M Young Mania Rating Scale, YMRS = 3.3, SD = 4.1, years ill M = 20.6, SD = 12.8, total episodes M = 62.9, SD = 104.3. The HDRS, YMRS, total episodes (depressive, manic, hypomanic), and years of illness were used as covariates so that a better estimate of the links between these candidate IPs and the genes of interest could be determined. Several recent meta-analyses of cognitive effects in BD as well as unaffected family members were the primary source of IP identification. When an IP was not present in these reviews, we relied on two other independent reports of significant differences between BD and HC groups (Mann-Wrobel et al., 2011; Bora, 2009, Torres et al., 2007). As the factors that we derived may combine some of these other measures, we elected to retain our factors to reduce the number of experimental tests/false positive rates (Langenecker et al., 2010). The dependent variables (candidate IPs) are four executive functioning factors (Processing Speed with Interference Resolution, Conceptual Reasoning with Set Shifting, Verbal Fluency with Processing Speed, Inhibitory Control), two memory factors (Auditory Memory and Visual Memory), two personality factors (Neuroticism and Conscientiousness), Fine Motor Dexterity factor, and an Emotion Processing Factor. Linear regression analyses were computed in two step models, with HDRS, YMRS, years ill, cumulative episodes, ethnicity (% European heritage), in the first step of the model, and additive regressor risk allele genotype for each of the respective SNPs in the second level of each model, respectively. Each regression was also repeated in only those with 100% European ancestry. Alpha was .05 for all analyses.
Results: The regression model was significant for SYNE1 when predicting the Processing Speed with Interference Resolution IP in the entire sample ($B = -.08$, $p = .04$). This full model included significant covariate effects of disease (case vs control, $B = -.24$, $p = 1.9^{10^{-5}}$), European heritage ($B = .12$, $p = .002$), and years ill ($B = -.15$, $p = .05$) with the Processing Speed with Interference Resolution IP. No other SNP by IP effects were significant. The relationship of SYNE1 with PSIR was not significant when only including those (cases and controls) with self-reported 100% parental European ancestry (n = 359, $B = -.07$, $p = .14$). When considering controls only, the model was stronger when only those of 100% European descent were considered (n = 92, $B = -.23$, $p = .03$ vs whole sample n = 158, $B = -.10$, $p = .20$). In cases, the effects of gene were not significant when the ethnic background was more homogeneous (100% European n = 273, $B = -.03$, $p = .63$) compared to the whole sample n = 445, $B = -.11$, $p = .02$). SNP effects in predicting case vs control status were not significant for SYNE1 ($B = -.04$, $p = .20$), Ankyrin3 ($B = -.03$, $p = .42$), or CACNA1C ($B = .01$, $p = .73$).
Conclusions: Common risk genes for mental illnesses such as BD, SCZ, and MDD likely contribute to more general IPs, yet these relationships are modest. As a result, deep phenotyping studies like the Prechter Longitudinal Bipolar Study can be effective in refining the IPS of interest, although ethnicity is an important factor in the model. The link between SYNE1 and a specific aspect of executive functioning, Processing Speed with Interference Resolution, signifies one of the strongest cognitive IPs present in affected cases and unaffected family members (Bora, 2009, Langenecket et al., 2010).
Keywords: genetics, bipolar, intermediate phenotypes
Disclosure: S. Langenecker, Nothing to Disclose; A. Vederman, Nothing to Disclose; S. Zoellner, Nothing to Disclose; M. Kamali, Nothing to Disclose; E. Saunders, Nothing to Disclose; M. McInnis, Nothing to Disclose; J. Zubieta, Nothing to Disclose; M. Burmeister, Nothing to Disclose.

T16. Novel Repeat Polymorphism in the Catechol-O-Methyltransferase (COMT) Gene: Association with Cocaine Dependence and Age-related Changes in Brain Metabolism

Elena Shumay*, Joanna Fowler, Nora D. Volkow

Brookhaven National Laboratory, Upton, New York

Background: Dopaminergic neurotransmission in brain reward circuits plays a major role in drug reward, abuse and dependence; therefore dopamine (DA) related genes are principal candidates for susceptibility to substance use disorders (SUD). The *COMT* gene is one of the most investigated in biological psychiatry since its product, catechol-O-methyltransferase metabolizes catecholamines, including DA. Multiple studies have examined the association of the functional Val158Met polymorphism with conditions of disrupted prefrontal activity, including psychiatric disorders (schizophrenia and addiction) and age-related cognitive decline. However, the role of the COMT in brain phenotypes beyond the prefrontal cortex remains unclear. Here we used *in silico* approach to identify new potentially variable regions in the COMT sequence and tested several putative polymorphisms to found a novel VNTR (variable number of tandem repeats) polymorphism which resides upstream of the 2nd exon. This VNTR has 67 bp period with the most common alleles having 1- and 2 repeats (1R and 2R) and produces three major genotypes 1R/1R; 1R/2R and 2R/2R. We investigated possible contribution of the new polymorphism to addiction by comparing genotype frequencies in cocaine abusers (CA, N = 181) and healthy controls (HC, N = 407) and explored genotype effect on brain function by considering differences in regional brain glucose metabolism measured with FDG-PET, which is a marker of brain function, between COMT_67 genotype groups comprised of healthy individuals.
Methods: 670 subjects were originally recruited to take part in imaging studies at BNL Imaging Center and also agreed to participate in the genetic study, providing a blood sample. Genotyping was performed by PCR with originally designed flanking primers and in house optimized conditions of amplification. PCR products were resolved using QIAxcel and individual genotypes were assigned based on the amplicon lengths. Validity and reproducibility of the genotyping was assured by repeated testing of the samples with more than 100 samples were tested in duplicates and triplicates. Analysis of the genotype frequencies within and between populations was carried out using SPSS. Brain glucose metabolic images (measured using PET and FDG) in HC (N = 122) who had participated as controls for studies that evaluated brain glucose metabolism during baseline conditions (no stimulation) were used to assess differences between genotypes (SPM-based analysis).
Results: In population, 1R and 2R alleles had comparable frequencies (76% and 67.5%, respectively) and 1R/2R genotype was predominant 45% along with homozygous carriers of 1R (31.3%) and 2R (22.7%). Rare allele with 3R was observed in 1% of individuals. Genotype frequencies significantly varied between ethnic groups ($\chi^2 = 98.3$, $p < 0.0001$). There were significant differences in allele- and genotype frequencies between CA (N = 181) and HC (N = 407): $\chi^2 = 8.93$, $p = 0.003$ *and* $\chi^2 = 13.5$, $p = 0.004$, respectively, wherein 2R-allele and 2R/2R genotype were more prevalent in CA than in HC. SPM analysis revealed higher metabolism in homozygous carriers of 2R-allele with significant differences in left superior temporal gyrus (voxel level

$p_{(FWEcorr.)} = 0.027$) and in left cuneus ($p_{(FWEcorr.)} = 0.045$). The COMT_67 genotype groups differ in respect to the age-dependent changes in brain metabolism: there were significant differences in regression slopes between the genotype groups (F-contrast) in left superior medial gyrus, left anterior cingulate cortex and right temporal lobe: (voxel level $p_{(FWEcorr.)} < 0.0001$). A decline in brain metabolism related to age was most evident in 1R2R genotype group (voxel-level $p_{(FWEcorr.)} = 0.001$ in left superior medial gyrus and right temporal lobe; and cluster-level (50) $p_{(corrected)} < 0.001$ in left superior medial gyrus, right temporal lobe and left caudate nucleus) contrasting less pronounces changes in groups of 1R1R and 2R2R individuals.
Conclusions: Our preliminary data suggest that the novel VNTR polymorphism in the COMT gene (COMT_67) that is not in LD with rs4680 (Val/Met polymorphism) can serve an informative marker for brain-related traits, including SUD and changes in regional brain metabolism associated with aging.
Keywords: imaging genetics, COMT, drug addiction, age-related changes in brain metabolism
Disclosure: E. Shumay, Nothing to Disclose; J. Fowler, Nothing to Disclose; N. Volkow, Nothing to Disclose.

T17. Common and Rare Gain-of-function Alleles of the Serotonin Transporter Gene, SLC6A4, Associated with Tourette Disorder

Pablo R. Moya*, Jens R. Wendland, Liza M. Rubenstein, Kiara R Timpano, Anne M. Andrews, Gary A. Heiman, Jay A. Tischfield, Robert A. King, Sammanda Ramamoorthy, Francis J. McMahon, Dennis L. Murphy

NIMH, NIH, Bethesda, Maryland

Background: Tourette disorder (TD) is a complex neurodevelopmental disorder characterized by chronic, fluctuating, involuntary motor and vocal tics. Comorbidity is a hallmark feature of TD, particularly with respect to obsessive-compulsive disorder (OCD) (~40-50%) and attention deficit hyperactivity disorder (ADHD) (~40%). TD and OCD may share some common familial and genetic factors.
Methods: Functional alleles in the serotonin transporter gene *SLC6A4* were evaluated in TD probands, relatives and controls (total European ancestry N = 1284). We genotyped the 5-HTTLPR, rs25531, rs25532 and the rare gain-of-function SERT I425V variant.
Results: The higher-expressing 5-HTTLPR/rs25531 L_A variant was more prevalent in TD probands than controls ($\chi^2 = 5.75$, $p = 0.017$, OR = 1.35), and significantly more frequent in probands with TD alone than in those with TD plus obsessive-compulsive disorder (OCD) (Fisher's exact test, $p = 0.0006$, OR = 2.29). The greater expressing L_{AC} haplotype (including rs25532) was more frequent in TD probands than controls ($p = 0.024$, OR = 1.33) and likewise in the TD alone group ($p = 0.0013$, OR = 2.14). Further, the rare gain-of-function SERT I425V coding variant was found in three male siblings with TD and/or OCD and their father. Two of these siblings and their father had a congenital renal/vesiculoureteral disorder. SERT I425V is associated with enhanced uptake, higher surface expression and loss of cGMP/PKG-mediated regulation. The cumulative count of SERT I425V thus becomes 1.57% in OCD/TD spectrum conditions vs. 0.15% in controls, with a recalculated, family-adjusted significance of $\chi^2 = 15.03$, $p < 0.0001$, OR = 9.0 (total N genotyped = 2914).
Conclusions: This first-reported large case-control study of *SLC6A4* variants in TD adds weight to the concept of greater SERT expression and function as a potential contributor to serotonergic abnormalities in TD. This report provides a unique combination of both common and rare variants in one gene in TD, all found to be associated with potentially causative *SLC6A4* over-expression and regulatory consequences.
Keywords: Tourette syndrome; serotonin transporter; SLC6A4; 5-HTTLPR; serotonin
Disclosure: P. Moya, Nothing to Disclose; J. Wendland, **Part 1:** Jens R. Wendland is a full-time employee of F. Hoffman-La Roche, Ltd. No conflict of interest for all other authors; L. Rubenstein, Nothing to Disclose; K. Timpano, Nothing to Disclose; A. Andrews, Nothing to Disclose; G. Heiman, Nothing to Disclose; J. Tischfield, Nothing to Disclose; R. King, Nothing to Disclose; S. Ramamoorthy, Nothing to Disclose; F. McMahon, Nothing to Disclose; D. Murphy, Nothing to Disclose.

T18. An American Genetic Variant of DISC1 Disrupts NDEL1 Binding and Phosphorylation in Human Induced Pluripotent Stem Cell Derived Neural Progenitors

Lindsay Wilson*, Sandra Engle, Zoe A. Hughes, Nicholas Brandon

Pfizer Inc, Cambridge, Massachusetts

Background: Major mental illness including schizophrenia, bipolar disorder, autism and depression are multifactoral diseases affected by both genetic and environmental factors. One genetic risk factor is disrupted in schizophrenia 1 (DISC1), a gene that was originally identified in a unique Scottish pedigree where a balanced chromosomal translocation and disruption of this gene segregates with mental disorders including depression, schizophrenia and bipolar disorder. DISC1 regulates multiple facets of neural function both in the developing and adult brain by binding to a multitude of signaling proteins collectively termed the DISC1 interactome. The discovery of DISC1 and its binding partners has illuminated the importance of this protein and their respective signaling pathways in disease. Even more importantly, they have aided in our understanding of how genetic variations in both DISC1 and DISC1 interacting proteins affect essential signaling pathways and cellular functions, and provide insight into the molecular mechanisms underlying psychiatric disease. Recently, a frameshift mutation in DISC1 resulting from a 4 bp deletion in exon 12 of DISC1 was identified in American family members diagnosed with either schizophrenia or schizoaffective disorder. This frameshift mutation results in a truncated protein and nine abnormal C-terminal amino acids which lie in the nuclear distribution element like-1 (NDEL1) binding domain. NDEL1, a known risk factor for psychiatric disease, plays an essential role in regulating the developing brain including neuron differentiation and migration and DISC1-NDEL1 interactions are required for neurite outgrowth. Currently, the functional consequences of the frameshift mutation in DISC1 are unknown.
Methods: To investigate the role of truncated DISC1 in cells we are utilizing neurons and neural progenitor cells differentiated from patient derived human induced pluripotent stem cells (iPSC). To fully understand the role of the 4 bp deletion in DISC1 we are also employing zinc finger nuclease technology to correct the mutated exon of DISC1 or mutating the correct exon in control iPS cells. This approach allows us to study the role of DISC1 in cells with an isogenic background. In addition to our cellular approach, biochemical and cell biological assays are used to investigate intracellular signaling pathways and protein binding.
Results: Immunoprecipitations demonstrate that truncated DISC1 can no longer bind to NDEL1 in cells. In addition to the binding defect, we observed that the phosphorylation pattern of NDEL1 is altered in cells expressing truncated DISC1. While NDEL1 has a prominent band shift in cells expressing wt DISC1, a single, non-phosphorylated NDEL1 species exists in truncated DISC1 expressing cells. Interestingly, treatment of wt DISC1 expressing cells with roscovitine, a CDK inhibitor, prevents phosphorylation of NDEL1 suggesting that by preventing NDEL1-DISC1 binding, NDEL1 function and regulation could be altered in these cells. Initial characterization of neural progenitors differentiated from iPSC demonstrates that DISC1 is expressed in neural progenitor cells, although there is a 90% ± 2% reduction in truncated DISC1 expression. In addition, NDEL1 and DISC1 interactions are abolished in mutant DISC1 cells suggesting that these cells will have altered NDEL1 functions.
Conclusions: Taken together, these initial observations suggest that truncation of DISC1 results in decreased NDEL1 binding and altered regulation and phosphorylation of NDEL1. In addition, utilization of iPS cells and zinc finger nuclease technology gives us

an opportunity to assess the role of truncated DISC1 using cells with an isogenic background allowing us to verify the consequences of specific DISC1 mutations while ruling out a potentially complex genetic background. These studies will aid in investigating the role of DISC1 in human neural progenitor cells, and human neurons and help to further understand signaling pathways implicated in psychiatric disease and provide possible new targets for drug development.
Keywords: DISC1, iPS cell neurons, schizophrenia
Disclosure: L. Wilson, Nothing to Disclose; S. Engle, Nothing to Disclose; Z. Hughes, Nothing to Disclose; N. Brandon, Nothing to Disclose.

T19. Analysis of Genetic Effects and Heritability of SNPs and Their Interactions in Two Ethnical Populations for Smoking Dependence

Ming D. Li*, Zhihong Zhu, Zhixiang Zhu, Jennie Z. Ma, Thomas J. Payne, Jun Zhu

University of Virginia, Charlottesville, Virginia

Background: With genome-wide and candidate gene-based association studies, numerous single nucleotide polymorphisms (SNPs) from different candidate genes are reported to be associated with nicotine dependence (ND). However, the contribution of each SNP and/or of interacting SNPs to ND is rarely addressed.
Methods: To determine the genetic contribution of each associated SNP and significant interacting SNPs to ND, we estimated genetic effects and heritability of SNPs that were reported to be associated with ND in our earlier studies andof significantly interacting two- and three-SNP combinations detected by generalized multifactor dimensionality reduction based on an exhaustively searching all possible two- and three-SNP combinations of 252 SNPs in 30 candidate genes.
Results: We revealed 9 SNPs in 5 genes (i.e., *CHAT, CRHR1, GABBR2, NRXN1*, and *TAS2R16*) have significant genetic effect on at least one ND measure in both AA and EA samples; 12 SNPs in 11 genes (i.e., *ANKK1, CHRNA3, CHRNA4, CHRNA5, DRD2, DRD3, GABBR2, GRIN3A, NRXN1, SHC3, and TAS2R38*) show significant effect on ND in the AA sample, and 5 SNPs in 4 genes (i.e., *DLG4, DRD2, GABBR2*, and *NRXN1*) show significant effect on ND in the EA sample, respectively. Further, we found that 10 two-interacting SNPs and 8 three-interacting SNPs also contribute significantly to ND.
Conclusions: We found these identified individual and interacting SNPs account 0.42, 0.58 and 0.57 of heritability for SQ, HSI and FTND, respectively. We conclude these detected significant individual SNPs and interacting SNP combinations account for about 2/3 and 1/3, respectively, of the detected heritability for these three ND measures.
Keywords: genetics, heritability, smoking, epistasis
Disclosure: M. Li, **Part 1:** N/A, **Part 2:** University of Virginia; ADial Pharceuticals LLC., **Part 4:** N/A; Z. Zhu, Nothing to Disclose; Z. Zhu, Nothing to Disclose; J. Ma, Nothing to Disclose; T. Payne, Nothing to Disclose; J. Zhu, Nothing to Disclose.

T20. The Effect of Distracting Noise on the Neuronal Mechanisms of Attention in Schizophrenia

Jason Tregellas*, Jason Smucny, Lindsay Eichman, Donald Rojas

University of Colorado School of Medicine, Aurora, Colorado

Background: The inability to ignore irrelevant environmental noise is a common problem for people with schizophrenia. The purpose of this study was to determine if the neuronal response to distracting noise is related to mechanisms of altered attention observed in the illness.
Methods: Twenty-two outpatients with schizophrenia and seventeen healthy comparison subjects performed a selective attention task in the presence or absence of distracting environmental noise while undergoing functional magnetic resonance imaging at 3T. A separate condition examining passive response to the distracting noise also was included.
Results: Group differences in neuronal response during the attention task were magnified by distracting noise, with the greatest difference being less response by patients, relative to comparison subjects, in the temporoparietal junction. Separate passive listening to distracting noise resulted in greater hippocampal response in patients, relative to comparison subjects. Across all subjects, hippocampal response to noise was inversely related to the degree to which the attention-task-related network was up-regulated to perform the task during distracting noise.
Conclusions: Given the observed hippocampal hyperactivity in response to environmental noise in patients and the inverse relationship between hippocampal response to noise and the effects of noise on the task-related network, hippocampal hyperactivity may contribute to impaired recruitment of attention networks in schizophrenia.
Keywords: schizophrenia, FMRI, hippocampus, attention
Disclosure: J. Tregellas, Nothing to Disclose; J. Smucny, Nothing to Disclose; L. Eichman, Nothing to Disclose; D. Rojas, Nothing to Disclose.

T21. Safety, Pharmacokinetic and Positron Emission Tomography Evaluation of Serotonin and Dopamine Transporter Occupancy Following Multiple-dose Administration of the Triple Monoamine Reuptake Inhibitor BMS-820836

Ming Zheng, Lieuwe Appel, Roger Lane, David Burt, Feng Luo, Robert Risinger, Gunnar Antoni, Matthew Cahir, Sanjay Keswani, Wendy Hayes, Zubin Bhagwagar*

Bristol-Myers Squibb, Wallingford, Connecticut

Background: The novel triple monoamine reuptake inhibitor BMS-820836 selectively inhibits the reuptake of the three monoamine neurotransmitters implicated in the pathophysiology of major depressive disorder: serotonin, norepinephrine, and dopamine. At the effective dose of 0.3 mg/kg orally in the mouse tail suspension model of depression, occupancy values were 86%, 76%, and 28% at the serotonin transporter (SERT), norepinephrine transporter (NET), and dopamine transporter (DAT), respectively, as measured in *ex vivo* binding experiments.[1] The aim of the present study was to determine the safety and tolerability, pharmacokinetic (PK) profile, and SERT and DAT occupancy using positron emission tomography (PET) following multiple daily doses of BMS-820836 in healthy volunteers.
Methods: Fifty-seven healthy volunteers (49 male; 8 female) were assigned to one of the following eight dose groups: 0.1, 0.25, 0.5, 1, or 2 mg/day without titration (24 male subjects); 3 or 4 mg/day with titration (13 male subjects); 1 mg/day without titration (6 female subjects) or placebo (12 male subjects; 2 female subjects). In each group, subjects received either BMS-820836 or placebo (3:1) as an oral daily dose for 14 days. Forty-two of the male subjects (33 BMS-820836; 9 placebo) participated in the PET study. SERT investigations (n = 12: 9 BMS-820836; 3 placebo) were conducted in the 0.1, 0.25, and 0.5 mg/day dose groups. DAT investigations (n = 30: 24 BMS-820836; 6 placebo) were conducted in the 0.5, 1, 2, 3, and 4 mg/day dose groups. BMS-820836 occupancy at SERT was determined using [^{11}C]MADAM[2], and at DAT using [^{11}C]PE2I[3] at 8 h post-dose (post-dose) on Day 10 and 24 h post-dose on Day 14 (i.e., Day 15). Blood samples were collected before and after each PET scan to determine the plasma concentrations of BMS-820836. Striatal SERT and DAT occupancies were estimated using a simplified reference tissue model[4] with cerebellum as reference region. Serial blood samples were also collected on Days 1 and 14, and trough blood samples were collected pre-dose on Days 5, 8,10, and 12 to characterize the PK of BMS-820836 and its active metabolite BMS-821007.
Results: Oral daily doses of BMS-820836 were generally well tolerated by the healthy subjects. There were no serious adverse events (AEs). Thirty-seven subjects (86%) who received BMS-820836 and 11 subjects (78.6%) who received placebo had one or more AEs during the study. The majority of AEs were mild and the

most common AEs overall were headache, fatigue, decreased appetite, and dizziness. Three subjects (BMS-820836, n = 2, male; placebo, n = 1, female) discontinued treatment due to moderate AEs. PK analyses showed that BMS-820836 had a median time to observed maximum concentration of 4.0–5.5 h and a mean apparent elimination half-life ranging from 44 to 74 h. BMS-820836 reached steady state by Day 10 following 0.1–2 mg daily, and Day 12 following 3 mg titration. The metabolite-to-parent ratio of the area under the concentration–time curve on Day 14 was 0.12. The analysis of PK data of BMS-820836 1 mg showed no evidence of sex differences. The target average striatal SERT occupancy of approximately 80% was achieved (individual range 74–84%) after multiple doses of BMS-820836 0.5 mg at both 8 h and 24–27 h post-dose. Moderate-to-high SERT occupancies (individual range 59–77%) were achieved after multiple doses of BMS-820836 0.1 and 0.25 mg/day at both time points. A near-linear relationship between dose and average DAT occupancy was observed for BMS-820836 from 1 mg to 3 mg at both 8 h and 24–30 h post-dose. For the higher doses of BMS-820836 3 and 4 mg/day, the average striatal DAT occupancies were 35% at 8 h post-dose and 30% for 24–30 h post-dose, whereas these values ranged between 14% and 30% for the 0.5-, 1-, and 2-mg doses.

Conclusions: Oral doses of BMS-820836 ranging from 0.1 mg to 4 mg were generally well tolerated by healthy subjects. The PK profile of BMS-820836 supports once daily administration. At doses of 0.5 mg/day, BMS-820836 demonstrated occupancy at SERT and DAT in the human brain consistent with known pharmacodynamic effects of antidepressant agents. Although NET human occupancy data for BMS-820836 are unavailable, the consistency between transporter occupancy in the mouse model and human occupancy of SERT and DAT suggest that human NET occupancy is potentially also in the same range as the SERT occupancy. These data suggest that BMS-820836 could be a promising, once-a-day, broad-spectrum antidepressant that can potentially provide symptomatic improvement in core depressive symptoms via modulation of serotonin, norepinephrine, and dopamine. BMS-820836 is currently in Phase 2 clinical development for the treatment of major depressive disorder that does not resolve with selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor therapy.

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Keywords: major depressive disorder, serotonin, dopamine, PET, triple monoamine reuptake inhibitor

Disclosure: M. Zheng, **Part 1:** I am a full time Bristol-Myers Squibb employee and receive salary and restricted stock, **Part 2:** Salary; L. Appel, Nothing to Disclose; R. Lane, **Part 1:** I am an employee of Bristol-Myers Squibb and have share options with that company, **Part 2:** My salary is paid by Bristol-Myers Squibb (for last 2 years) and I have exercised share options in Bristol-Myers Squibb in excess of $10,000 during 2012, **Part 3:** Bristol-Myers Squibb; D. Burt, **Part 1:** Currently employed at Bristol-Myers Squibb, **Part 2:** Bristol-Myers Squibb, **Part 3:** Currently employed at Bristol-Myers Squibb; F. Luo, **Part 1:** employee of BMS, **Part 2:** employee of BMS, **Part 3:** employee of BMS, **Part 4:** N/A; R. Risinger, **Part 1:** Johnson & Johnson, Bristol-Myers Squibb, Alkermes plc, **Part 2:** Johnson & Johnson, Bristol-Myers Squibb, Alkermes plc, **Part 3:** Bristol-Myers Squibb, Alkermes plc, **Part 4:** None; G. Antoni, Nothing to Disclose; M. Cahir, Nothing to Disclose; S. Keswani, **Part 1:** I am a full-time employee of Bristol-Myers Squibb, **Part 2:** I am a full-time employee of Bristol-Myers Squibb, **Part 3:** I am a full-time employee of Bristol-Myers Squibb ie. 100% of my income, **Part 4:** I am a full-time employee of Bristol-Myers Squibb; W. Hayes, **Part 1:** I am an employee of BMS and own BMS stock, **Part 2:** I am an employee of BMS and own BMS stock, **Part 3:** I am an employee of BMS and own BMS stock; Z. Bhagwagar, **Part 1:** Full Time Employee at Bristol-Myers Squibb, Own BMS stock, **Part 2:** Full Time Employee at Bristol-Myers Squibb, Own BMS stock, **Part 3:** Full Time Employee at Bristol-Myers Squibb, Own BMS stock.

T22. Differential Control of Learning and Anxiety along the Dorso-ventral Axis of the Dentate Gyrus

Mazen A. Kheirbek*, Liam J. Drew, Daniel Costantini, Nesha Burghardt, Lindsay Tannenholz, Susanne E. Ahmari, Hongkui Zeng, Andre Fenton, Rene Hen

Columbia University, New York, New York

Background: The hippocampus, in addition to its role in learning and memory, is increasingly implicated in the pathophysiology of anxiety disorders. The hippocampus shows marked variation along its dorso-ventral axis in terms of both afferent and efferent connectivity, yet it is unclear if this heterogeneity mediates its differential contributions to memory processing and to anxiety-like behavior, whether the three primary subregions of the hippocampus (dentate gyrus, CA3 and CA1) perform the same operations along the dorso-ventral axis, or if real-time activity changes in the hippocampal circuitry can acutely affect emotional state. Granule cells (GCs) of the dentate gyrus subregion of the hippocampus are implicated in affective processing, as they are especially susceptible to damage by elevated stress hormone levels, and adult neurogenesis, a unique feature of the DG, modulates emotional states and is required for some of the behavioral effects of antidepressants. To test the specific contribution of DG GCs to emotional behavior we examined the effects of acutely increasing or decreasing activity in DG GCs in tests of cognition and mood.

Methods: We used optogenetic techniques to modulate activity in DG GCs in real-time. To target opsin expression selectively to GCs we used a POMC-Cre line crossed to conditional eNpHR3.0-EYFP and ChR2-tdTomato lines. Mice were implanted with fiber optics targeted to either the dorsal or the ventral DG, and tested for behavioral effects of light induced inhibition or excitation. To test the role of DG GCs in learning and anxiety-like behavior, mice were tested in contextual fear conditioning, active place avoidance, elevated plus maze and open field test.

Results: Dependent on their position along the dorso-ventral axis of the hippocampus, GCs control specific features of anxiety-related behavior and contextual learning. In mice expressing eNpHR3.0 in the DG, inhibition GCs in the dorsal, but not ventral, DG blocks the encoding, but not the retrieval, of contextual fear memories and the rapid and flexible encoding of spatial information in active place avoidance, while having no effect on anxiety-related behaviors. In contrast, elevating the activity of GCs in the dorsal DG with ChR2 resulted in a dramatic increase in exploratory behavior, while elevating activity in the ventral DG powerfully suppressed innate anxiety.

Conclusions: By using optogenetic techniques that allow neural activity in DG GCs to be acutely, reversibly and bidirectionally manipulated, this study supports the hypothesis that the dorsal and ventral poles of the hippocampus are functionally distinct and demonstrates that hippocampal activity not only has a mnemonic function but can also strongly influence anxiety-related behaviors. Specifically, dorsal GCs were shown to contribute to spatial and contextual learning, where they were required for rapid encoding of contextual information, but not for memory retrieval. Surprisingly, elevating dorsal DG activity also induced a dramatic increase in exploratory behavior in novel environments. The ventral DG was not required for contextual fear learning, but was found to exert a major influence on innate anxiety-like behavior. Recent studies employing deep brain stimulation to ameliorate symptoms of treatment resistant depression highlight the effectiveness of circuit based approaches for the treatment of psychiatric illness. Our results provide the first evidence that increasing activity in the ventral DG can reduce innate anxiety without affecting learning. The clear dissociation between the contributions of the dorsal and ventral poles of the DG to cognitive function and anxiety offers a rationale for pursuing strategies that target the ventral DG to treat anxiety with minimal cognitive side effects.

Keywords: dentate gyrus, anxiety, fear learning, optogenetics

Disclosure: M. Kheirbek, Nothing to Disclose; L. Drew, Nothing to Disclose; D. Costantini, Nothing to Disclose; N. Burghardt, Nothing to Disclose; L. Tannenholz, Nothing to Disclose; S. Ahmari, Nothing to Disclose; H. Zeng, Nothing to Disclose; A. Fenton, Nothing to Disclose; R. Hen, **Part 1:** Lundbeck & Roche.

T23. Anxiety Delays the Development of Fear Inhibition in Children at High Risk for Trauma Exposure

Tanja Jovanovic*, Telsie Davis, Ami Smith, Jennifer Winkler, Seth D. Norrholm, Kerry J. Ressler, Bekh Bradley

Emory University School of Medicine, Atlanta, Georgia

Background: Our previous studies with traumatized adult populations showed that PTSD patients with the highest symptoms have impaired inhibition of fear-potentiated startle in the presence of safety cues (Jovanovic et al., 2009; Norrholm et al., 2010). The current study aimed to investigate whether this psychophysiological phenotype is a biomarker of anxiety in children growing up in high trauma environments.
Methods: The study sample was recruited from a highly traumatized urban population at Grady Hospital in Atlanta, GA. We recruited 8-to-12-year-old children ($n = 38$) and their mothers. We measured fear-potentiated startle during a differential fear conditioning task with a danger cue and a safety cue, using electromyographic recordings of the eyeblink muscle. The paradigm included colored shapes as conditioned stimuli and an aversive airblast as the unconditioned stimulus. The session was similar to those we have used previously in adults (Jovanovic et al., 2011), except that the airblast pressure was reduced. Child anxiety symptoms were assessed with parent and child report interviews using the Behavioral Assessment System for Children, 2nd edition (BASC-2; Reynolds & Kamphaus, 2004). Child trauma exposure was assessed using the Violence Exposure Scale for Children-Revised (VEX-R; Fox & Leavitt, 1995).
Results: All children showed significant fear-potentiated startle to the danger signal predicting the airblast $F(1,34) = 6.45$, $p < .02$, and significant discrimination between danger and safety, $F(1,34) = 5.68$, $p = .02$. However, fear-potentiated startle to the safety signal was negatively correlated with child age ($r = -.33$, $p < .05$) and positively correlated with anxiety ($r = .32$, $p < .05$). When we categorized the children according to age and anxiety, we found that discrimination between danger and safety was significant only in children 10 years or older, $F(1,27) = 9.99$, $p = .004$, and children with low anxiety, $F(1,18) = 9.05$, $p = .008$. Moreover, younger children with low anxiety had similar fear responses to older children, but those with high anxiety showed the highest fear-potentiated startle to the safety signal (i.e. the least fear inhibition). Degree of child trauma exposure was also correlated with anxiety ($r = .43$, $p = .007$), but not fear-potentiated startle. The association between child anxiety and fear inhibition remained significant after co-varying for degree of trauma exposure ($r = .33$, $p < .05$).
Conclusions: These preliminary results suggest that inhibition of fear-potentiated startle in the presence of safety cues develops with age andreaches adult-like levels around 10 years of age. Anxiety symptoms may disrupt this developmental trajectory and reduce the ability to appropriately inhibit fear responses. This deficit may increase vulnerability for PTSD and other anxiety disorders in children who are already at greater risk for trauma exposure. The proposed method provides a laboratory paradigm that iswell-tolerated in school age children with trauma exposure, yet results in a robust measure of fear responses. Thus, it is a promising translational tool that can detect early biomarkers of anxiety in children.
Keywords: Child Development, Anxiety, Trauma, Fear Conditioning, Fear-potentiated startle
Disclosure: T. Jovanovic, Nothing to Disclose; T. Davis, Nothing to Disclose; A. Smith, Nothing to Disclose; J. Winkler, Nothing to Disclose; S. Norrholm, Nothing to Disclose; K. Ressler, Nothing to Disclose; B. Bradley, Nothing to Disclose.

T24. A Non-competitive NMDA Antagonist AZD6765 Compared with Ketamine and Placebo on Pharmaco-MRI and Cognitive Mechanistic Biomarkers in Untreated Major Depressive Disorder; a Randomized Double-blind Controlled Trial

Bill Deakin*, Steve Williams, Darragh Downey, Shane McKie, Guy Goodwin, Angela Rylands, Catherine Harmer, Kevin Craig, Colin Doursih, Gerard Dawson, Dennis McCarthy, Mark A. Smith

University of Manchester, Manchester, United Kingdom

Background: Overactivity of the subgenual cingulate (SGC) cortex has been described in depression, which is reported to normalise with recovery. Recently a pharmacoMRI (phMRI) study revealed that an i.v. bolus of ketamine induced a rapid decrease in blood oxygenation level dependent (BOLD) signal in the SGC in healthy volunteers (Deakin et al., 2008). We investigated whether AZD6765, in development as an antidepressant, and ketamine share effects on SGC BOLD signal when administered as a slow infusion. Effects on cognitive fMRI biomarkers for antidepressant activity were evaluated 24hrs later.
Methods: Sixty males or females aged 18 to 45 years with major depressive disorder were randomly assigned to three groups to receive (i.v.) ketamine, AZD6765 or saline during a 60 min phMRI scan. Twenty-for hours later, behavioural and fMRI responses to emotional faces, emotional Stroop and memory tasks were recorded. The study was carried out in Manchester and Oxford, UK.
Results: Contrary to prediction, in both study sites the active drugs gradually increased the SGC BOLD signal; no decreases were seen in any other region. The SGC was the only area in which phMRI responses predicted improvement in Montgomery-Asberg mood ratings scale 1 and 7 days post-infusion of the active drugs. Interviewer-rated psychotic (BPRS) and dissociative symptoms were minimal and not statistically significant following administration of AZ6765. Improvement in individual self- rated depression (BDI) scores seen the day after infusion (day 2) correlated only with SGC (BA25) and anterior cingulate (BA32) within the whole brain. These relationships held for BDI improvement 7 days after infusion. Both drugs reduced amygdala responses to fear and sadness in the emotional faces task 24hrs post-infusion.
Conclusions: The absence of an acute de-activation following ketamine infusion suggests this is only seen with the rapidly rising ketamine concentrations and more intense subjective effects induced by bolus infusion. Activation of the SGC was seen following two different NMDA compounds in both Manchester and Oxford using different 3T MRI machines and this effect predicted improvement in mood 1 and 7 days post infusion. Furthermore, we previously reported SCG activation after i.v. citalopram (McKie et al., 2005). The findings suggest that SGC may be a site of initiation of antidepressant responses. Amygdala responses to emotional faces were attenuated 1 day after pretreatment with AZ6765 and to a lesser extent after ketamine. This property is shared by a variety of antidepressants in patients and healthy volunteers and in the absence of, or prior to changes in mood (Murphy et al., 2009). The results suggest that AZ6765 and ketamine have antidepressant –like effects on emotion processing in the brain, that actions on the SGC may initiate these effects and that diminished NMDA glutamate neurotransmission is the immediate mechanism as both drugs share this property. Deakin JFW et al. Archives of General Psychiatry 2008;65:154 64. McKie S et al. Psychopharmacology. 2005; 180:680-6 Murphy SE et al. British Journal of Psychiatry. 2009; 194:535-540.
Keywords: ketamine depression pharmaco-MRI sub-genual cingulate cortex glutamate
Disclosure: B. Deakin, **Part 1:** The University of Manchester is reimbursed for advisory boards and speaking for Johnson & Johnson, Servier, Roche, AstraZeneca, **Part 4:** Research grants from AstraZeneca; Servier; Lundbeck; P1vittal; Medical Research Council; National Institure for Health Reseach; S. Williams, **Part 4:** Grant from AstraZeneca; D. Downey, Nothing to Disclose; S. McKie, Nothing to Disclose; G. Goodwin, **Part 4:** Grants from

P1Vital, Sanofi-Aventis, Servier, Baily Thomas Charitable Fund, Economic and Social Research Council and Medical Research Council.; A. Rylands, Nothing to Disclose; C. Harmer, **Part 1:** Advisory panel of P1vital and owns shares in the company. She has also acted as a consultant for P1vital and Servier and has undertaken paid speaking engagements for astra zeneca, Eli-Lilly and Lundbeck. She is a company director and shareholder of Oxford Psychologists. Paid consultant for Lundbeck and Merck Sharp & Dohme and is on the advisory board of P1vital, **Part 4:** Grants from P1vital; K. Craig, Nothing to Disclose; C. Doursih, **Part 2:** Shareholder in P1vital; G. Dawson, **Part 3:** Shareholder in P1vtal; D. McCarthy, **Part 3:** Full time AstraZeneca employee; M. Smith, **Part 2:** Full time employee at AstraZeneca.

T25. Ghrelin Intravenous Administration Increases Alcohol Craving in Alcohol-Dependent Individuals: Preliminary Findings from a Human Laboratory Study

Lorenzo Leggio*, William Zywiak, Samuel Fricchione, Steven Edwards, Robert Swift, George Kenna

SCPN/LCTS, NIAAA/NIDA, NIH, Bethesda, Maryland

Background: Ghrelin is a gut peptide acting as the endogenous ligand for the growth hormone secretagogue receptor (GHS-R), and able to control appetite and food intake. Consistent with the known evidence that food- and alcohol-seeking behaviors share the same neurobiological pathways, it has been suggested that ghrelin may play a role in alcohol dependence (AD). For example, in mice peripheral or central ghrelin administration results in increased alcohol intake in a 2-bottle free-choice paradigm, as well as in increased locomotor stimulation, accumbal dopamine release and conditioned place preference. In humans, both our group and others have tested endogenous ghrelin levels, and reported that active drinking alcohol-dependent (AD) patients have lower plasma ghrelin when compared to controls; baseline ghrelin levels may predict subsequent alcohol drinking or abstinence, and correlates positively with psychometric measurements of alcohol craving. However, while the previous human studies have been testing endogenous ghrelin levels, for the first time by any researchers, we have examined the effects of an acute administration of human ghrelin intravenous (i.v.) upon craving in AD individuals. **Methods:** The design was a double-blind, placebo-controlled randomized human laboratory study, testing an acute intravenous (IV) administration of ghrelin 1 mcg/kg, ghrelin 3 mcg/kg, or a saline solution (placebo). Participants were non-treatment seeking AD heavy drinkers. Participants rated alcohol craving on an 11-point Visual Analogue Scale (VAS) prior to the injection, and during a first and second alcohol cue-reactivity (CR) procedure, after being exposed to visual, tactile, olfactory, and proprioceptive stimuli associated with alcohol beverage. In addition, participants completed a 45-item adverse events (AEs) measure on a 4-point scale prior to the injection, during each of the CR procedures, and following the second CR procedures. The sample ($n = 12$) consisted of 36% females, 64% White subjects with an average age of 42.7 (9.5) years with a mean onset of alcohol problems at age 19.6 (3.7). **Results:** A repeated measures ANOVA (between subjects factor: drug condition, within subjects factor: CR procedures) revealed a significant increase in VAS score craving for ghrelin high dose versus ghrelin low dose versus placebo [$F(2,20.9) = 3.75$, $p = .04$]; increase in craving was significantly greater in both the 1 mcg/kg [$F(1,13.8) = 6.23$, $p = .03$] and the 3mcg/kg ghrelin condition [$F(1,13.0) = 8.03$, $p = .01$] relative to the placebo condition. When the two ghrelin groups were combined, there was also a statistically significant difference versus placebo [$F(1,20.8) = 7.48$, $p = .01$]. To evaluate differences in AEs the mean intensity across the 45 items was calculated, a repeated measures ANCOVA was conducted which included the baseline AE intensity as a covariate and the three post injection AE scores as the repeated dependent measure. There were no significant differences across all ghrelin/placebo conditions when all 3 [$F(2,12.3) = 0.54$, $p = .60$] or the first 2 post injection AE scores were examined [$F(2,17) = .96$, $p = .40$]. All AE summary scores were well under the mild rating (1.0) across the different group X time cells (greatest mean = .089).
Conclusions: This is the first human study testing the effects of human ghrelin administered IV to AD subjects. In addition to pointing out the safety of ghrelin administered IV to AD people, this translational research represents the first demonstration that the acute administration of human ghrelin IV, as compared to placebo, results in a significant increase in alcohol craving. This human study is consistent with the previous animal studies testing the effects of ghrelin administration in mice, as well as with our previous clinical studies showing that AD patients with higher plasma ghrelin levels have higher craving, as assessed by psychometric assessments. This research adds the first direct demonstration that pharmacologically-induced high ghrelin levels, via an acute administration of human ghrelin IV increase significantly alcohol craving. Notably, alcohol craving was tested in 'real time' (right after ghrelin/placebo administration), using a validated CR procedure, and under a well-controlled human lab environment. These results suggest that pharmacotherapies aimed at antagonism of the ghrelin system may represent a novel approach for AD patients. *Supported by NIH/NIAAA grant R21-AA019709 (Brown University; PI: Leggio).*
Keywords: alcoholism, ghrelin, cue-reactivity,
Disclosure: L. Leggio, **Part 1:** Advisory Board member for D&A Pharma; Advisor for CT San Remo; W. Zywiak, Nothing to Disclose; S. Fricchione, Nothing to Disclose; S. Edwards, Nothing to Disclose; R. Swift, **Part 1:** Advisory Board member for D&A Pharma; Advisor for CT San Remo; G. Kenna, **Part 1:** Advisor for CT San Remo.

T26. Later Dinnertime Is Associated with Abdominal Obesity in Patients with Bipolar Disorder

Isabella Soreca*, Ellen Frank, David J. Kupfer

Univeristy of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Background: Patients with bipolar disorder (BD) have high rates of obesity and Metabolic Syndrome. Considering the wealth of data documenting cardiovascular disease (CVD) morbidity and mortality in BD, there has been surprisingly little research investigating the causes and mechanisms leading to increased cardiovascular risk other than the reported effects of psychotropic medications. While medications undoubtedly play a major role, a number of neurobiological and behavioral characteristics linked to BD may independently increase CVD risk. For example, we have shown that evening chronotype, sleep duration, and season of birth are associated with the cardiovascular profile in patients with BD. Evening chronotype, a frequent behavioral trait in patients with BD, is associated with greater social rhythm irregularities, including later and more variable meal timing and higher body fat percentage. Therefore, we hypothesized that evening chronotype may increase CVD risk in BD through behavioral mechanisms such as irregular/misaligned meal timing. The goal of this study was to explore the association between timing of the evening meal and abdominal obesity, independent of other lifestyle factors, in a sample of patients with bipolar disorder type I in clinical remission.
Methods: Methods: All the experimental procedures were reviewed and approved by the University of Pittsburgh Institutional Review Board. Participants were 114 males and females with Bipolar I disorder in clinical remission, all of whom were overweight or obese by WHO criteria (BMI $\geqslant 25$) at study entry. All patients were on standard of care medications for BD. Dinner times were obtained with the Pittsburgh Sleep Diary (PSD). Metabolic syndrome and its components were defined according to the ATP III NCEP criteria. To determine the best way to calculate the central tendency of dinner time over one week of diary, we first created a histogram of the week of dinner time observations. Because of between and intra-subject variability, we chose to use the median and standard deviation to summarize the week of observed dinner time for each individual.

Non-parametric tests were used to compare patients with and without abdominal obesity and the other components of the metabolic syndrome on age, psychotropic medications, median dinner time and its standard deviation. Since there was no differences in these parameters based on other components of metabolic syndrome than abdominal obesity, a logistic regression model was then built to evaluate the contribution of median dinner time and its standard deviation to the likelihood of having abdominal obesity, first, and to BMI after controlling for age, sex, and median sleep duration obtained with the PSD. These covariates were selected based on univariate association with the outcome variable in this sample and also based on *a priori* knowledge of risk factors for abdominal obesity.
Results: Despite the fact that all study participants were overweight or obese, only 67% had abdominal obesity. Patients with abdominal obesity had dinner roughly one hour later than patients without abdominal obesity. Median dinner time was significantly associated with abdominal obesity (ExpB = 1.7; p = 0.047), independent of age, sex and sleep duration. The risk of having abdominal obesity increases by roughly 14% with every 30 minutes of delayed dinner time.
Conclusions: Animal studies have shown that caloric intake during the biological night has detrimental effects on glucose tolerance and weight gain, independent of total caloric intake. Misalignment between social and circadian rhythms can therefore have adverse consequences on health. Patients with bipolar disorder may often incur in this scenario because of their frequently chaotic and irregular lifestyles In this report we show that the timing of the evening meal is associated with the likelihood of having abdominal obesity In this population.
Keywords: bipolar disorder, abdominal obesity, social rhythms, meal timing
Disclosure: I. Soreca, Nothing to Disclose; E. Frank, **Part 1:** Servier International Advisory Board, **Part 2:** Guilford Press and American Psychological Association Press Royalties; D. Kupfer, Nothing to Disclose.

T27. Differential Maturation of Subtypes of Perisomatic GABAergic Inputs in Monkey Prefrontal Cortex

Gil D. Hoftman*, Kenneth Fish, David A. Lewis

University of Pittsburgh, Pittsburgh, Pennsylvania

Background: The presence of cognitive disturbances during childhood in individuals who are diagnosed with schizophrenia later in life suggests that the illness is a disorder of neurodevelopment. These cognitive deficits reflect, at least in part, altered prefrontal cortex (PFC) activity due to impaired GABA neurotransmission. Thus, studying the normal development of PFC GABA circuits is important for understanding illness pathogenesis. In primate PFC, the densities of both glutamate and GABA synapses peak at ~3 mo postnatal. Glutamate synapses are substantially pruned during adolescence. In contrast, GABA synapses do not appear to undergo massive pruning during the same time period. However, the detectability of certain pre- and post-synaptic markers at parvalbumin-immunoreactive (PV-IR) chandelier neuron (PVch) to the axon initial segment (AIS) of pyramidal neurons (PYR) is decreased between 3 mo and adult monkeys. Although these developmental findings could result from protein expression changes in morphologically intact PVch connections, they might represent the elimination of a subset of these connections over development. To differentiate between these possibilities and compare PVch development against other GABA inputs to the perisomatic region (proximal dendrites, soma and AIS) of PYR, we assessed the apposition density and relative synaptic protein levels of 1) PVch, 2) PV-IR basket neurons (PVb), and 3) PV-immunonegative basket neurons ($PV_{neg}b$).
Methods: Multi-label fluorescence confocal microscopy was used to assess perisomatic innervation of PYR neurons in superficial and middle layers of the PFC from monkeys ranging in age from postnatal 1 week to adult (n = 3 per group x 7 groups), in order to define changes in pre- (vesicular GABA transporter [vGAT] and PV) and postsynaptic ($GABA_A$ receptor γ2 subunit [γ2]) proteins in PVch, PVb and $PV_{neg}b$ to PYR appositions. PVch appositions were defined as vGAT-IR puncta overlapping γ2-IR puncta contained within ankyrin-G (AnkG)-IR AISs. PVb appositions were defined as vGAT-IR/PV-IR overlapping puncta that overlapped γ2-IR puncta contained within neuronal nuclei (NeuN)-IR somata. $PV_{neg}b$ appositions were defined as PV-negative, vGAT-IR puncta overlapping γ2-IR puncta contained within NeuN-IR somata.
Results: The mean number of PVch appositions per AnkG-IR AIS significantly decreased between 3 mo and adult monkeys. Relative mean vGAT and PV protein levels per PVch apposition did not differ across the same time period. Analyses between superficial and middle layers revealed that relative protein levels of vGAT, but not PV, per PVch apposition were significantly greater in the middle layers of 3 mo monkeys, while no laminar difference in relative vGAT or PV protein levels was seen in adults. In contrast to PVch appositions, neither the density of PVb appositions nor that of $PV_{neg}b$ appositions per NeuN-IR soma differed between 3 mo and adult animals. Also unlike PVch appositions, relative mean PV protein levels per PVb apposition significantly increased, and relative mean vGAT protein levels per $PV_{neg}b$ apposition significantly increased between 3 mo and adult animals. For 3 mo but not adult animals, relative levels of PV protein in PVb appositions were increased in the middle versus superficial layers, while those of vGAT protein did not differ. For $PV_{neg}b$ appositions, relative vGAT protein levels did not differ between superficial and middle layers in 3 mo and adult animals. Postsynaptically, relative γ2 protein levels did not differ across layer or age at any of the 3 apposition subtypes.
Conclusions: In the monkey PFC, PVch appositions were selectively eliminated between 3 mo and adult animals. The elimination of PVch, but not of PVb or $PV_{neg}b$, appositions suggests a cell type-specific functional maturation of GABA synapses. Consistent with this interpretation, presynaptic protein levels differed with age and cortical layer across subtypes of perisomatic appositions, with $PV_{neg}b$ appositions reaching adult levels before PVch and PVb appositions. In concert, these findings suggest that perisomatic inputs from different types of GABA neurons have distinct roles in the maturation of PFC circuit function, and thus might be expected to be differentially involved in the pathophysiology of cognitive dysfunction in schizophrenia. Quantitative analyses in other developmental age groups are ongoing and will be presented at the meeting.
Keywords: Development, Parvalbumin, GABA, Confocal Microscopy, Chandelier Cell
Disclosure: G. Hoftman, Nothing to Disclose; K. Fish, Nothing to Disclose; D. Lewis, **Part 1:** Consultant for Bristol-Myers Squibb, **Part 4:** BMS foundation, Bristol-Myers Squibb, Curridium Ltd, Pfizer.

T28. Adjunctive AZD6765, a Low-trapping NMDA Channel Blocker, in Treatment-resistant Major Depressive Disorder: A Randomized, Placebo-controlled Study

Gerard Sanacora*, Mark A. Smith, Sanjeev Pathak, Hong-Lin Su, Dennis McCarthy

Yale University, New Haven, Connecticut

Background: Several small randomized, placebo-controlled and open-labeled studies have provided strong evidence that ketamine, an *N*-methyl-D-aspartate receptor (NMDAR) antagonist, induces a rapid and robust antidepressant effect in a proportion of patients who had not responded to existing antidepressant drugs. The interpretation of these studies and the clinical utility of this approach have been limited by the acute psychological and physiological effects associated with ketamine that lead to incomplete study-drug blinding and problems transitioning treatment to the clinic setting. AZD6765, an NMDA channel blocker with distinct pharmacological properties, including low-channel trapping, appears to be associated with minimal psychotomimetic effects at the doses studied in early phase I and IIa studies. AZD6765 demonstrates clear antidepressant effects in rodent models historically associated with both antidepressant and anxiolytic efficacy, and phase IIa studies suggest a single i.v. dose of AZD6765

has transient antidepressant effects in patients with treatment-resistant depression. This study was designed to determine whether repeated administration of AZD6765 would help extend and consolidate the antidepressant effects and evaluate the safety of repeated dosing.

Methods: A phase IIb, multicenter, double-blind, randomized study (NCT00781742). Key inclusion criteria: Outpatients aged 18-65 years with DSM-IV-TR-diagnosed major depressive disorder (MDD) and a history of poor response to $\geqslant 2$ antidepressants. The study consisted of a screening period (up to 30 days) and a 3-day placebo run-in, where patients received a single-blind placebo (0.9% saline solution) infusion. Patients were randomized to 3-week treatment with AZD6765 100 mg, AZD6765 150 mg, or placebo (3 i.v. infusions/week) as adjunct to current antidepressant therapy, followed by 5-week follow-up. Primary efficacy endpoint: Change from randomization to Week 3 in MADRS total score. Secondary variables included MADRS score change at other scheduled assessments, remission (ie, MADRS score $\leqslant 10$), response (ie, $\geqslant 50\%$ reduction from baseline in MADRS score), HAM-A (anxiety), HAM-D and QIDS-SR-16 (depressive symptoms), Bond-Lader VAS (alertness and calmness), CGI-S and CGI-I (global improvement), and Q-LES-Q-SF (quality of life) during treatment and follow-up. Changes in QIDS-SR-16 score at Day 1 and in MADRS score at Day 3 were measured. Safety and tolerability assessments included adverse events during treatment and follow-up, dissociative state assessed by Clinician Administered Dissociative States Scale (CADSS), and suicidality assessed by the Beck Scale for Suicide Ideation (BSS) and Columbia Suicide Severity Rating Scale (C-SSRS).

Results: 152 patients were randomized to AZD6765 100 mg ($n = 51$), AZD6765 150 mg ($n = 51$), or placebo ($n = 50$), with mean baseline MADRS scores of 33.3, 34.1, and 33.5, respectively. At Week 3, AZD6765 100 mg and 150 mg reduced MADRS total scores from randomization significantly more than placebo (-13.4 [$p = 0.006$] and -12.7 [$p = 0.019$] vs -7.9, respectively). Both AZD6765 100 mg and 150 mg groups showed significant improvements versus placebo on HAM-A, CGI-S, and CGI-I scales by Week 3. Moreover, the AZD6765 100 mg group showed significant improvements versus placebo on response rate, HAM-D, QIDS-SR-16, and Q-LES-Q-SF scales. There were no significant differences between AZD6765 and placebo groups in QIDS-SR-16 score at Day 1 or in MADRS score at Day 3. However, the antidepressant efficacy achieved at Week 3 persisted for several weeks after stopping AZD6765 treatment. The most frequent adverse event during AZD6765 treatment was mild and transient dizziness. No serious adverse events were reported during the treatment period. Incidences of suicidal ideation and suicidal behavior, assessed by C-SSRS, were similar between AZD6765 and placebo groups. AZD6765 produced no clinically meaningful difference compared with placebo on dissociative symptoms as measured by CADSS. In addition, both AZD6765 and placebo groups showed reduced suicidal ideation and dissociative symptoms at Week 3 versus baseline, as assessed by BSS and CADSS, respectively.

Conclusions: This study demonstrates the antidepressant efficacy of repeated administration of AZD6765 over a 3-week period. The findings are important as they provide the first evidence of a sustained antidepressant response associated with repeated administration of an NMDAR antagonist in a placebo-controlled trial. Moreover, AZD6765 had minimal acute psychological and physiological effects on patients in the study, suggesting the blind was successfully maintained and demonstrating the ability to divorce the antidepressant action of an NMDAR antagonist from the unwanted psychotomimetic effects. The inability to demonstrate statistically significant antidepressant effects versus placebo over the first 3 days may reflect the increased magnitude of placebo response in this study or the distinct properties of AZD6765 compared with ketamine. In summary, this is the first placebo-controlled study to show that the antidepressant effect of an NMDAR antagonist can be safely extended for a period of weeks with repeated administration.

Keywords: NMDA, glutamate, antidepressant, Depression, AZD6765

Disclosure: G. Sanacora, **Part 1:** AstraZeneca Pharmaceuticals, Avanier Pharmaceuticals, Bristol-Myers Squibb, Evotec, Eli Lilly & Co., Hoffman La-Roche, Novartis, and Novum Pharmaceuticals, **Part 4:** AstraZeneca, Bristol-Myers Squibb, Johnson and Johnson, and Hoffman La-Roche, Merck & Co.; M. Smith, Nothing to Disclose; S. Pathak, **Part 1:** Employee of AstraZeneca Pharmaceuticals, **Part 2:** Employee of AstraZeneca Pharmaceuticals, **Part 3:** Employee of AstraZeneca Pharmaceuticals, **Part 4:** Employee of AstraZeneca Pharmaceuticals; H. Su, **Part 1:** Employee of AstraZeneca Pharmaceuticals, **Part 2:** Employee of AstraZeneca Pharmaceuticals, **Part 3:** Employee of AstraZeneca Pharmaceuticals, **Part 4:** Employee of AstraZeneca Pharmaceuticals; D. McCarthy, **Part 1:** Employee of AstraZeneca Pharmaceuticals, **Part 2:** Employee of AstraZeneca Pharmaceuticals, **Part 3:** Employee of AstraZeneca Pharmaceuticals, **Part 4:** Employee of AstraZeneca Pharmaceuticals.

T29. TRPA1 "Menthol Preference" Haplotypes are Associated with Levels of TRPA1 Expression and Smoking Cessation Success

George Uhl*, Donna Walther, Frederique Behm, Jed Rose

NIH/JHUSM, Baltimore, Maryland

Background: Among smokers, there are substantial individual differences in preference for mentholated brands of cigarettes and abilities to quit smoking. Menthol exerts complex species specific actions at transient receptor potential (TRP) channels that include the TRPA1 channel that is likely to mediate many mentol effects in plumonary afferents. Animals with reduced TRPA1 expression display substantially-reduced resonses to noxious cigarette smoke and its constituents (eg acrolein). We have recently reported association of a TRPA1 haplotype with menthol preference in each of two independent samples of European-American smokers (Uhl et al, 2011). This haplotype is defined by a missense SNP and 10 intronic SNPs whose minor alleles confer $>$ 1.3 odds ratio of menthol preference in heavier ($>$ 15 cigarettes/day) smokers, and more modest influences in lighter smokers. We now report association of tis haplotype with levels of expression of TRPA1 and with ability to quit smoking in two clinical trial samples.

Methods: Genotypes from smokers who participated in each of two smoking cessation clinical trials and maintained continuous biochemically-verified abstinence for at least 11 weeks bwyond the targeted quit date were compared to those of individuals who were abstinent at neither 4 nor 11 weeks, but who were matched for European-Amerian ancestry, gender, and arm of the study. Genotypes were performed using DNA extracted from blood using a mass spec/primer extension method. Allele specific expression was performed using RT PCR identification of allele-specific amplimers in mRNA extracted from 30 ventral medullary samples from heterozygous individuals.

Results: mRNA from the major haplotype of TRPA1 was expressed at significantly higher levels than that expressed from the minor haplotype. Homozygous indivduals thus differ by about 25% in TRPA1 expression. The TRPA1 menthol preference haplotype was present at significantly higher frequencies in successful quitters than in unsuccessful matched nonquitters. These differences were highly signifiant in the combined samples.

Conclusions: These results improve our understanding of TRPA1 quit success haplotypes. They document influences on levels of expression. SNPs studied here are iin strong linkage disequilibrium witth other intronic and missense SNPs, including those that have recently been shown to influence TRPA1 regulation by cold (May et al, 2012) and other missense SNPs. The data provide links between individual difference, menthol preferences among smokers and ability to quit smoking that have both scientific and regulatory implications. SInce menthol preference and frequencies of the "menthol preference" haplotypes are both higher in African Americans, extension of this work will be important to understand such links in individuals from this racial/ethnic background.

Keywords: Smoking cessation, genetics of gene expression, ethnic differences, menthol preference

Disclosure: G. Uhl, Nothing to Disclose; D. Walther, Nothing to Disclose; F. Behm, **Part 2:** Duke University, Patent royalties to spouse, **Part 4:** Spouse license of device patent Phillip Morris International; J. Rose, **Part 2:** Duke University, Patent royalties, Consulting, **Part 4:** Licensing of device patent to Phillip Morris International.

T30. Gene Expression Profiling in Selectively Bred Rat Lines that Differ in Addiction Liability

Shelly B. Flagel*, Maria Waselus, Stanley J. Watson, Robert Thompson, Huda Akil

University of Michigan, Ann Arbor, Michigan

Background: Many people are exposed to addictive drugs throughout the course of their lives, but few become addicts. What renders some individuals more susceptible to addiction remains to be determined, but most would agree that there is no single trait or gene underlying the disorder. We have spent the last several years studying rats that are selectively bred for differences in locomotor response to novelty and have found that these animals differ on a number of traits related to addiction. Relative to selectively-bred low-responder rats (bLRs), bred high-responder rats (bHRs) exhibit increased locomotor response to novelty, increased risk-taking behavior, higher susceptibility to control by reward-related cues, increased impulsivity, increased aggression and hypersensitivity of their dopamine system. When we examined whether bHR rats are more susceptible to addiction, we found that, relative to bLRs, bHRs: 1) self-administer cocaine at a faster rate during the early phase of drug-taking behavior; 2) show greater susceptibility to control by drug-associated cues; 3) are more likely to seek drug when it is no longer available; and d) show greater propensity for both cue- and drug-induced reinstatement, or relapse. Thus, we took advantage of this unique genetic animal model to examine the neurobiological antecedents and consequences of addictive behavior. We used a "discovery" based approach to examine thousands of genes simultaneously and to identify patterns or profiles of gene expression that may contribute addiction liability.
Methods: bHR and bLR rats from the 26th generation of an in-house selective breeding colony were used. All rats were initially screened for locomotor response to novelty to confirm their phenotype. A subset of rats was sacrificed following locomotor testing and brains were obtained to examine "basal" differences in gene expression. Another group of rats underwent jugular catheterization surgery and were trained to self-administer cocaine. Self-administration sessions were conducted in such a way that all rats received the same number of infusions and drug-cue pairings throughout the study, which lasted for approximately 60 days. Tests were conducted throughout the paradigm to examine the effects of cue-removal on drug-taking behavior and the persistence of drug-seeking behavior when the drug was no longer available. Drug-induced reinstatement was examined following 1 week of abstinence and cue-induced reinstatement after 1 month of abstinence. Rats were sacrificed and brains were obtained 1 week after the final cue-induced reinstatement test. Laser capture microdissection (LCM) was combined with microarray gene chip technology (Affymetrix Rat Gene 1.0 ST Array) to characterize "basal" gene regulation (i.e. antecedents) and gene regulation following prolonged self-administration experience (i.e. consequences) in the core and shell of the nucleus accumbens and in the prelimbic cortex of bHR and bLR rats.
Results: The prolonged self-administration paradigm implemented in this study allowed us to conclude that bHR rats are more susceptible to addiction, and especially to relapse, relative to bLR rats. Thus far we have examined gene expression profiles in the core of the nucleus accumbens in bHR vs. bLR rats under "basal" conditions and following the prolonged cocaine self-administration paradigm that resulted in "addictive behavior" in bHRs, but not bLRs. After applying filtering criteria related to expression values, fold change and statistical significance, our final analyses were conducted on close to 300 genes for the basal time point and 400 genes for the post self-administration time point. Analyses were conducted using Ingenuity Pathway Analysis tools. Although the design of the study does not allow for direct comparison between the basal vs. post self-administration time points, a number of pathways were found to significantly differ between phenotypes under one condition, but not the other. For example, "glucocorticoid receptor signaling" was identified as a pathway that differed robustly between phenotypes following the self-administration paradigm, but to a much lesser degree under basal conditions. Moreover, there are a number of addiction-related molecules that appear to differ between phenotypes in either one or both conditions. Among these molecules are the kappa 1 opioid receptor, dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32), and other signaling molecules related to cyclic-AMP (cAMP), mammalian target of rapamycin (mTOR) and Fibroblast Growth Factor (FGF) pathways. Validation of these results using qPCR is ongoing, and preliminary data look promising.
Conclusions: Our previous studies suggest that bHR rats represent those individuals at one extreme of the population that may be highly susceptible to addiction, whereas bLR rats may represent individuals at the other extreme who are resilient to the disorder. Here we used a "discovery" driven approach in hopes of identifying differences in gene expression between bHRs vs. bLRs under basal conditions and following prolonged cocaine exposure in brain regions associated with the "reward pathway". Although analyses and validation of the results are ongoing, it is hoped that the results will identify: 1) potential candidate genes that might predispose an individual to vulnerability to addiction and 2) novel targets for the pharmacological treatment of addiction.
Keywords: individual differences, cocaine, microarray gene expression, rats, addiction
Disclosure: S. Flagel, Nothing to Disclose; M. Waselus, Nothing to Disclose; S. Watson, Nothing to Disclose; R. Thompson, Nothing to Disclose; H. Akil, Nothing to Disclose.

T31. Just C NO to DREADDs: Inhibition of Ventral Pallidum Projection to Ventral Tegmental Area Blocks Cue-triggered Cocaine Seeking

Stephen V. Mahler*, Elena M. Vazey, Jennifer Kaufling, Gary Aston-Jones

Medical University of South Carolina, Charleston, South Carolina

Background: Designer receptors exclusively activated by designer drugs (DREADDs) are synthetic G-protein coupled receptors that are inert, except in the presence of their agonist, CNO (which is inert in the absence of DREADDs). DREADD-expressing neurons can therefore be experimentally controlled in a highly selective, "lock-and-key" manner. Although light-activated opsins are preferable for experiments requiring precise temporal (milliseconds to seconds) control of neuronal activity, DREADDs can be preferable when extended periods of inactivation are desired (minutes to hours). In addition, DREADDs do not require tethering of animals to a light source, an advantage when animals perform complex behaviors.
Methods: Here, we examined the role of ventral pallidum (VP) and its projection to ventral tegmental area (VTA) in reinstatement of cocaine seeking. We used an hM4D Gi-coupled DREADD construct, expressed under control of a synapsin promoter via lentiviral neurotransduction *in vivo* in rats. First, we examined the necessity of VP for reinstatement elicited by either cocaine-associated cues or a cocaine priming injection. We bilaterally transfected VP neurons with the DREADD viral vector, trained rats on cocaine self-administration and extinction, and then and systemically administered several doses of the DREADD agonist CNO during cue-induced or cocaine primed reinstatement sessions. We found that CNO dose-dependently blocked cue-induced, but not cocaine-primed reinstatement of cocaine seeking, indicating that VP activity is required for cues to trigger cocaine seeking.
Results: We previously observed that VP projections to VTA are robustly Fos activated during cue-induced reinstatement behavior,

so we next sought to examine whether this specific projection is necessary for cue-induced reinstatement of cocaine seeking. For this, we again bilaterally transfected VP neurons with the hM4D DREADD, allowed time for DREADD transport to axonal terminals in VTA (2-3 weeks), and implanted bilateral cannulae into VTA. Prior to cue-induced or cocaine-primed reinstatement sessions, we microinjected CNO into VTA to specifically inhibit DREADD-expressing VP terminals. Again, this attenuated cue-induced, but not cocaine-primed reinstatement.
Conclusions: These findings demonstrate that i) DREADDs are a useful means of modulating neuronal activity in behavioral experiments, ii) DREADDs can be used to locally inhibit terminals of projections from transduced neurons, and iii) ventral pallidum projections to VTA are crucial for cue-induced, but not cocaine-primed reinstatement. Supported by PHS grants R37 06214 and F32 DA026692.
Keywords: addiction, mesolimbic, dopamine, RASSL, relapse
Disclosure: S. Mahler, Nothing to Disclose; E. Vazey, Nothing to Disclose; J. Kaufling, Nothing to Disclose; G. Aston-Jones, Nothing to Disclose.

T32. DLPFC Hyperactivation is Associated with the mir137 Schizophrenia Risk Genotype

Steven Potkin*, Theo Van Erp, Ilaria Guella, Marquis P. Vawter, Federica Torri, Judith M. Ford, Kelvin O. Lim, Juan Bustillo, Ayse Belger, Adrian Preda, Dana Nguyen, Jessica Turner, Daniel H. Mathalon, Fabio Macciardi

UCI, Irvine, California

Background: Aberrant dorsolateral prefrontal cortex (DLPFC) activation, as measured using functional magnetic resonance imaging (fMRI) during working memory processing, is a robust correlate of schizophrenia. Consistent with DLPFC inefficiency in schizophrenia, we have shown DLPFC hyper-activation in schizophrenia patients compared with controls even when task performance in patients and controls is equivalent[1]. We have identified several genetic polymorphisms that are associated with DLPFC activation[2, 3] and subsequently identified several micro RNAs based on a gene set enrichment analysis[4]. These micro RNAs included mir137, which was recently confirmed to play an etiological role in schizophrenia based on a very large genome-wide case-control association study[5]. Combined these studies implicate mir137-dysregulation in the etiology of schizophrenia and suggest that mir13 7 may be involved in regulating DLPFC activation. In this study we directly examine the association between the mir137 schizophrenia risk genotype and DLPFC activation.
Methods: Functional magnetic resonance imaging scans were acquired from 50 schizophrenia patients and 66 age and sex-matched healthy volunteers who performed a Sternberg Item Response Paradigm. The paradigm includes loads of 1, 3, and 5 items. Dorsolateral prefrontal cortex (DLPFC) retrieval activation for the working memory load of 3 items, for which hyperactivation had been shown in schizophrenia patients compared with controls, were obtained from the previously published data set[1]. MIR137 SNP (rs1625579) was genotyped (schizophrenia/healthy volunteers: GG n = 0/n = 2, GT n = 10/n = 15, TT n = 40/49). We conducted a Fisher's Exact Test toe examine the distributions of MIR137 (rs1625579) alleles across diagnoses and a mixed model regression analysis to examine the effects of diagnosis and genotype on DLPFC activation while controlling for effects of sex, age and site.
Results: MIR137 risk (rs1625579 T) allele distributions were equivalent between patients and healthy volunteers. Schizophrenia patients had significantly higher DLPFC activations compared with controls. Independent of diagnosis, the MIR137 TT genotype was associated with significantly higher DLPFC activations compared with the combined GG and GT genotypes.
Conclusions: The mir137 TT schizophrenia risk genotype[4, 5] is associated with DLPFC hyper-activation, a known schizophrenia risk phenotype and a measure of brain inefficiency. These findings suggest that functional implications of mir137 gene-regulation are measurable with fMRI even at relatively modest sample sizes and that the mir137 gene regulatory networks merits further investigation with regard to its etiological role in schizophrenia. For more RNA expression results see Vawter et al. (abstract submitted to this meeting). 1. Potkin, S.G., et al., *Working memory and DLPFC inefficiency in schizophrenia: the FBIRN study*. Schizophr Bull, 2009. **35**(1): p. 19-31. 2. Potkin, S.G., et al., *A genome-wide association study of schizophrenia using brain activation as a quantitative phenotype*. Schizophr Bull, 2009. **35**(1): p. 96-108. 3. Potkin, S.G., et al., *Gene discovery through imaging genetics: identification of two novel genes associated with schizophrenia*. Mol Psychiatry, 2009. **14**(4): p. 416-28. 4. Potkin, S.G., et al., *Identifying gene regulatory networks in schizophrenia*. Neuroimage, 2010. **53**(3): p. 839-47. 5. Ripke, S., et al., *Genome-wide association study identifies five new schizophrenia loci*. Nat Genet, 2011. **43**(10): p. 969-76.
Keywords: Mir137 fMRI schizophrenia risk
Disclosure: S. Potkin, **Part 1:** Bristol-Myers Squibb, Eisai, Inc., Eli Lilly, Forest Laboratories, Genentech, Janssen Pharmaceutical, Lundbeck, Merck, Novartis, Organon, Pfizer, Roche, Sunovion, Takeda Pharmaceutical, Vanda Pharmaceutical, **Part 2:** Lundbeck, Merck, Novartis, Sunovion, **Part 3:** Lundbeck, Merck, Novartis, Sunovion, **Part 4:** Amgen, Baxter, Bristol-Myers Squibb, Cephalon, Inc., Eli Lilly, Forest Laboratories, Genentech, Janssen Pharmaceutical, Merck, Novartis, Otsuka, Pfizer, Roche, Sunovion, Takeda Pharmaceutical, Vanda Pharmaceutical, NIAAA, NIBIB, NIH/NCRR, University of Southern California, UCSF, UCSD, Baylor College of Medicine; T. Van Erp, Nothing to Disclose; I. Guella, Nothing to Disclose; M. Vawter, Nothing to Disclose; F. Torri, Nothing to Disclose; J. Ford, Nothing to Disclose; K. Lim, Nothing to Disclose; J. Bustillo, Nothing to Disclose; A. Belger, Nothing to Disclose; A. Preda, Nothing to Disclose; D. Nguyen, Nothing to Disclose; J. Turner, Nothing to Disclose; D. Mathalon, **Part 1:** Consultant to BristolMyersSquibb Inc.; F. Macciardi, **Part 1:** TEVA.

T33. Common Genetic Variation within Transcription Factor Binding Sites is Associated with Bipolar Disorder

David TW. Chen*, Nirmala Akula, Liping Hou, Girma Hawariat, Sevilla Detera-Wadleigh, Xueying Jiang, BiGS Consortium, Francis J. McMahon

National Institute of Mental Health, Bethesda, Maryland

Background: Genome-wide association studies(GWAS) have uncovered several loci associated with bipolar disorder (BD), but functional alleles have not been identified. Some GWAS signals may reflect genetic variation in sequences that regulate gene expression via binding of transcription factors. This study tested the hypothesis that signals obtained via GWAS reflect genetic variation in transcription factor binding sites (TFBS).
Methods: Genetic association data was extracted from ameta-analysis of worldwide GWAS in BD comprising ~14,000 cases and controls. This set of over 700,000 single nucleotide polymorphisms (SNPs) was mapped onto published TFBS identified in human lymphoblastoid cells. Enrichment for bipolar GWAS signal among SNPs near TFBS was tested with the Kolmogorov-Smirnov (K-S) rank-sum statistic, accounting for linkage disequilibrium via PLINK(v1.07) SNP pruning. Empirical p-value was determined by permutation. SNP allele frequency bias was tested using XLSTAT. Exploration for biological function among these TFBS genetic variations most enriched for GWAS signals was performed using two independent approaches: 1. INRICH (atgu.mgh.harvard.edu/inrich/); 2. GREAT(http://great.stanford.edu/public/html/index.php), DAVID(david.abcc.ncifcrf.gov/summary.jsp).
Results: There was a significant enrichment of GWAS signals (empirical $p = 9.1x10^{-3}$) among SNPs near TFBS. This enrichment was not attributable to linkage disequilibrium between SNPs or allele frequencies among SNPs detected in the GWAS. Genes near these SNPs significantly clustered into relatively few functional pathways ($p < 0.05$), especially the serine/threonine protein kinase

pathway. This clustering was not explained by gene size, variable assignment of SNPs to nearby genes, or linkage disequilibrium among SNPs. Three genes emerged most often, DDR1, MAP3K5, RAF1.
Conclusions: These results suggest that common alleles that contribute to risk for BD reflect, in part, genetic variation in TFBS that regulate gene expression. Further studies of gene expression and its genetic regulation are warranted in BD.
Keywords: bipolar disorder, transcription factor binding sites, common genetic variations
Disclosure: D. Chen, Nothing to Disclose; N. Akula, Nothing to Disclose; L. Hou, Nothing to Disclose; G. Hawariat, Nothing to Disclose; S. Detera-Wadleigh, Nothing to Disclose; X. Jiang, Nothing to Disclose; B. Consortium, Nothing to Disclose; F. McMahon, Nothing to Disclose.

T34. Are Endophenotypes of Schizophrenia More or Less Heritable than the Disorder Itself in the COGS-1 Family Study?

Gregory A. Light*, Tiffany A. Greenwood, Daniel J. Mathias, Neal R. Swerdlow, David L. Braff, COGS Investigators

VISN-22 Mental Illness, Research, Education, and Clinical Center (MIRECC), San Diego VA Health Care System; University of California San Diego, La Jolla, California

Background: Twin studies have previously estimated the heritability of schizophrenia to be as high as 81%. The NIMH Consortium on the Genetics of Schizophrenia (COGS-1) is a family study designed to use neurocognitive and neurophysiologic endophenotypes to deconstruct the complex genetic architecture of schizophrenia via heritability and genetic linkage and association analyses. Across the 12 endophenotypes assessed, heritability estimates ranged from 18% to 50% (mean = 30%). Since ascertainment strategy may have influenced the heritability estimates, the aims of the present study were to estimate the heritability of diagnosis of schizophrenia and related serious mental illnesses in both the sample of individuals who underwent endophenotypes testing and, secondarily, the first degree relatives of directly interviewed participants.
Methods: Each of the 296 families consisted of a schizophrenia proband, one clinically unaffected sibling and both parents (n = 1366 total subjects, mean family size = 4.6). Additional affected and unaffected siblings where included whenever possible, and families missing one or both parents were accepted if one or two additional siblings were available. These nuclear families were included in a recent study of endophenotype heritability and linkage. The Diagnostic Interview for Genetic Studies (DIGS) was used to confirm a proband diagnosis of schizophrenia (SZ) or schizoaffective disorder (SZA). The Family Interview for Genetic Studies (FIGS) was also administered to all participating family members (n = 1337) in order to obtain convergent psychiatric symptom information in first-degree relatives of directly interviewed individuals. Using this information from the FIGS, we were able to substantially extend the nuclear families with consensus psychiatric diagnoses for additional family members (n = 2292, mean family size = 7.7). Heritability estimates of psychiatric diagnoses were obtained for the nuclear and extended families using methods consistent with those used previously to assess the endophenotypes.
Results: With ascertainment that emphasized inclusion of discordant siblings, the heritability of SZ, including SZA, was estimated as 0% in the COGS-1 nuclear families and 1% in the extended families. When lifetime history of other serious mental illnesses were included (ie. SZ, SZA, bipolar disorder, or major depressive disorder), heritability estimates were 37% in the nuclear and 15% in the extended families (p's < 0.002).
Conclusions: Endophenotypes related to schizophrenia and other serious mental illnesses are at least as heritable as the disorders themselves in the COGS-1 family sample and offer promise for filling the gene-to-phene knowledge gap. The absolute lack of heritability and obvious discrepancy between previously reported heritability estimates of SZ is thought provoking. While higher heritability estimates in schizophrenia were derived primarily from twin studies, the COGS-1 ascertainment scheme focused on the recruitment of intact families with sibling pairs discordant for SZ in order to provide greater phenotypic contrast between and among the siblings. Although our ascertainment strategy resulted in lower heritability estimates for schizophrenia than those observed in twin studies, endophenotype heritability remained at significant levels. The higher heritability observed when the phenotype was broadened to include other serious mental illnesses suggests that these illnesses may reflect variable expressivity and shared genetic susceptibility with schizophrenia in these COGS-1 families.
Keywords: Endophenotypes, Schizophrenia, heritability, cognitive, genetics, neurophysiology
Disclosure: G. Light, Nothing to Disclose; T. Greenwood, Nothing to Disclose; D. Mathias, Nothing to Disclose; N. Swerdlow, **Part 1:** Dr. Swerdlow has received unrelated compensation for consulting services funding from Neurocrine; D. Braff, Nothing to Disclose; C. Investigators, **Part 1:** Dr. Green has received unrelated support for consulting services from Abbott, Amgen, Cypress, Lundbeck, Shire and Teva, and he has been a speaker for Otsuka and Sunovion, Dr. Freedman has a patent through the Department of Veterans Affairs on DNA sequences in CHRNA7, Drs. Cadenhead, Calkins, Dobie, Radant, Schork, Seidman, Siever, Silverman, Stone, Sugar, DW Tsuang, and MT Tsuang report no financial relationships with commercial interests, **Part 4:** Dr. Nuechterlein has received unrelated research support from Ortho-McNeil Janssen Scientific Affairs and has consulted to Wyeth/Pfizer, Dr. Olincy has received unrelated research support from Lundbeck Pharmaceuticals, Drs. Gur and Turetsky have received unrelated research support for investigator-initiated grants from Pfizer and AstraZeneca.

T35. Epigenetic Modulation of the Leukocyte Glucocorticoid Receptor and Childhood Parental Loss

Audrey R. Tyrka*, Carmen Marsit, Lawrence H. Price, Yuliya I. Kuras, Noah S. Philip, Linda L. Carpenter

Brown Medical School / Butler Hospital, Providence, Rhode Island

Background: Adult psychopathology is often preceded by a history of early adverse experiences. Epigenetic changes to genes that regulate stress reactivity have been proposed as a mechanism of this effect. Work in rodents links low maternal care to greater methylation of the promoter region of the glucocorticoid receptor (GR) gene in hippocampus. Recent human studies of post-mortem hippocampus and umbilical cord blood also suggest that promoter methylation of GR (NR3C1) is associated with early adverse exposures. We recently reported preliminary findings of greater leukocyte NR3C1 promoter methylation in association with childhood parental loss (n = 22). In the present study we tested these associations in an expanded sample of 43 subjects with childhood parental loss, and tested for effects specific to parental death and parental desertion.
Methods: Healthy adults without current major Axis I disorder, including 23 with parental death, 24 with parental desertion and 76 with no loss, participated in this study. DNA was extracted from frozen whole blood. Sodium bisulfite modification of DNA was performed and methylation at the NR3C1 promoter region was examined with a quantitative pyrosequencing approach at four previously identified CpG sites. Multivariate analyses of covariance (MANCOVA) were used to test effects of parental loss, and separately parental death and parental desertion, on percent methylation at the four CpG sites, controlling for effects of age.
Results: Participants with childhood parental loss had greater NR3C1 promoter methylation overall at the four sites (p = .001), and *post hoc* analyses showed significant effects at CpG 1 (p < .001), CpG 3 (p < .005), and CpG 4 (p = .05). *Post hoc* analyses of each type of loss showed that parental death was associated with significantly greater methylation at CpG 1,3, and 4, and parental desertion was significantly predictive of increased methylation at CpG 1 and 3. Additional post-

hoc analyses controlling for effects of childhood abuse and neglect among those with a history of parental loss, suggested unique effects of parental death, but not parental desertion.
Conclusions: These findings suggest that childhood parental loss may lead to epigenetic modifications of the human GR gene which could partially underlie the associations between childhood adversity and risk for psychopathology. Parental death appears to have unique epigenetic effects beyond those seen with childhood maltreatment, whereas the effect of desertion may not be separable from the effect of childhood maltreatment.
Keywords: epigenetics methylation early-life stress parental loss
Disclosure: A. Tyrka, **Part 1:** Medtronic, Neuronetic, NeoSync, Lundbeck, **Part 4:** Medtronic, Neuronetic, NeoSync; C. Marsit, Nothing to Disclose; L. Price, **Part 1:** Gerson Lehrman, Wiley, Springer, Qatar National Research Fund, Alberta Heritage Foundation for Medical Research, Abbott, AstraZeneca, Neuronetics, Cyberonics, Medtronic, Neosync, **Part 4:** Medtronic, Neuronetics, Neosync, Cyberonics; Y. Kuras, Nothing to Disclose; N. Philip, **Part 1:** Neuronetics, **Part 4:** Neuronetics; L. Carpenter, **Part 1:** Abbott, Helicon, Johnson & Johnson, Takeda Lundbeck, Neuronetics, Cyberonics, Medtronic, Neosync, **Part 4:** Neuronetics, Cyberonics, Medtronic, Neosync.

T36. Excess Homozygosity in the MHC in Schizophrenia

Semanti Mukherjee, Saurav Guha, Anil Malhotra, Itsik Pe'er, Ariel Darvasi, Todd Lencz*

Feinstein Institute for Medical Research, Glen Oaks, New York

Background: The major histocompatibility complex (MHC) region on chromosome 6 has been associated with schizophrenia in genome wide association studies (GWAS). Notably, GWAS to date have generally focused on additive allelic effects. However, the ecological literature suggests that homozygosity at the MHC locus may be associated with vulnerability to disease. We applied a novel approach to study homozygosity in the MHC region in an ethnically homogenous schizophrenia case-control cohort to understand the etiology of schizophrenia.
Methods: We genotyped 904 schizophrenia cases and 1640 healthy controls drawn from the Ashkenazi Jewish (AJ) population using the Illumina HumanOmni1-Quad array. Phased (using Beagle 3.0) genotype data was processed with GERMLINE and DASH algorithms (under default parameters) to perform pairwise comparisons across all chromosomes, thereby identifying chromosomal segments (haplotypes) shared identical-by-descent (IBD). We extracted all such segments shared IBD across at least 3 chromosomes in our dataset, and compared homozygosity at such segments in cases and controls. We focused on specifically on data for the extended MHC locus (chr6: 25Mb-35Mb).
Results: We found a significant excess of homozygosity in schizophrenia cases compared to controls in the MHC ($p = 2.2e-16$, $OR = 1.3$). By contrast, amount of homozygosity-by-descent was relatively equal across the rest of the genome ($OR = 0.98$). Within the extended MHC locus, we observed that most of the homozygous regions which were over-represented in cases relative to controls were located within the classical MHC class I and class II regions. Results were replicated in an independent case-control schizophrenia cohort of Japanese ancestry.
Conclusions: Homozygosity in the classical MHC region appears to convey significant risk for schizophrenia. Lack of diversity of MHC alleles may predispose to enhanced susceptibility to prenatal infection.
Keywords: genetics, schizophrenia, major histocompatibility complex
Disclosure: S. Mukherjee, Nothing to Disclose; S. Guha, Nothing to Disclose; A. Malhotra, **Part 1:** Genomind, Shire, Eli Lilly, Sunovion, Abbott, **Part 2:** Genomind, **Part 4:** Abbott; I. Pe'er, Nothing to Disclose; A. Darvasi, Nothing to Disclose; T. Lencz, **Part 1:** Consultant, Eli Lilly.

T37. Antipsychotic-induced Metabolic Abnormalities in Schizophrenia: The Prominent Role of Appetite Regulating Hypothalamic Genes

Daniel J. Mueller*, Arun K. Tiwari, Nabilah I. Chowdhury, Natalie Freeman, Jeffrey A. Lieberman, Herbert Y. Meltzer, James L. Kennedy

University of Toronto and Centre for Addiction and Mental Health, Toronto, Ontario, Canada

Background: The substantial inter-individual variability observed in response and side effects with antipsychotic drugs is likely to largely depend on genetic factors. One of the most debilitating side effects, emerging with many newer antipsychotic drugs, is substantial weight gain associated with cardiovascular complications and metabolic syndrome. We have been dedicating our efforts to investigate genetic causes in the serious side effect of antipsychotic induced weight gain. We have recently unravelled several important hypothalamic gene variants of the leptin-melanocortin energy homeostasis system associated with antipsychotic-induced weight gain. Here we investigated new variants in the melanocortin-3 receptor (MC3R) and the neuropeptide Y 2-receptor (NPY2R) genes.
Methods: A total of 237 patients who underwent treatment for chronic schizophrenia or schizoaffective disorder were evaluated for antipsychotic response and induced weight gain for up to six months. The sample consisted mainly of individuals of European descent exposed to clozapine for their first time. Ten SNPs in the MC3R gene and 15 SNPs in the NPY2R gene were genotyped. SNPs were selected for having a minor allele frequency of at least 5% and in order to allow for a dense coverage, regions 10 kb upstream and 2 kb downstream of both genes were included. In addition, SNPs were selected based on their functional relevance reported in the literature.
Results: Our analyses with the MC3R gene showed that three SNPs were significantly associated with percentage of weight gain in treated patients of European ancestry. Specifically, carriers of the AA genotypes in SNP rs3746619 ($p = 0.04$), rs 1543570 ($p = 0.03$) and rs6014649 ($p = 0.02$) were at higher risk to gain almost twice the amount of weight following treatment with clozapine or olanzapine.
Our analyses with the NPY2R gene showed that patients of European ancestry who were treated with clozapine or olanzapine and who were carriers of the T-allele of SNP rs12507396 gained on average significantly more weight than non-carriers ($p = 0.025$). This result became even more significant when we corrected for duration of treatment ($p = 0.01$). Haplotype analyses and findings in the other remaining SNPs yielded some interesting trends which will be discussed.
Conclusions: Our results tentatively suggest novel associations between functionally relevant markers of the MC3R and NPY2R genes in schizophrenic patients treated with antipsychotic medication associated with high risk for metabolic abnormalities and weight gain. Replications are warranted to minimize risk for spurious findings and thus we are currently performing replication studies in samples of schizophrenia patients who were prospectively assessed over a longer time period. If replicated, these findings will help to create clinical algorithms to identify patients at higher risk for antipsychotic-induced weight gain through personalized medicine. However, further work is needed in order to further understand the functional role of gene variants in MC3R and NPY2R gene variants in antipsychotic-induced weight gain.
Keywords: schizophrenia, antipsychotics, genetics, weight gain, hypothalamus
Disclosure: D. Mueller, Nothing to Disclose; A. Tiwari, Nothing to Disclose; N. Chowdhury, Nothing to Disclose; N. Freeman, Nothing to Disclose; J. Lieberman, **Part 1:** In the past three years JAL reports having received research funding or is a member of the advisory board of Allon, Alkermes Bioline, GlaxoSmithKline Intracellular Therapies, Lilly, Merck, Novartis, Pfizer, Pierre Fabre, Psychogenics, F. Hoffmann-La Roche LTD, Sepracor (Sunovion) and Targacept. JAL receive no direct financial compensation or salary

support for participation in these researches, consulting, or advisory board activities; H. Meltzer, **Part 1:** Board Membership – Acadia, Consultancy- Sunovion Novartis, Janssen, Acadia, Teva, Lilly, Jazz Pharmaceuticals, Employment- Suregene, Expert Testimony - Janssen, Grants/Grants Pending - Sunovion Novartis, Dainippon Sumitomo, Envivo, Lilly, Payment for Lectures Including Service on Speakers Bureaus – Sunovion, Novartis, Patents (Peninf, Planned or Issued)- Dainippon Sumitomo, Payment for Development of Educational Presentations - Teva, Stock/Stock Options - Acadia, Glaxo, Advisor/Researcher - Centerstone Research Institute; J. Kennedy, **Part 1:** JLK has been a consultant to GSK, Sanofi-Aventis, and Dainippon-Sumitomo.

T38. eQTLs are Conserved across Brain Regions and Inform Genetic Association Results of Bipolar Disorder

Margit Burmeister*, Viktoriya Strumba, Benjamin Keller, Ellen Schmidt, Matthew Flickinger, Elsbieta Sliwerska, Alan F. Schatzberg, Jack Barchas, William E. Bunney, Richard M. Myers, Stanley J. Watson, Jun Li, Laura Scott, Michael Boehnke, Huda Akil

University of Michigan, Ann Arbor, Michigan

Background: Genetic association findings for psychiatric disorders have been of modest effect size, and often identify genetic variants (SNPs) that do not affect protein structure, and whose functionality is hence difficult to understand. Expression quantitative trait loci (eQTLs) are genetic variants that affect gene expression, specifically, cis eQTLs are loci that affect the expression of a nearby gene. To assess the regulatory effect of SNPs in different brain regions, we determined the genotypes of ~2.5 million SNPs and assessed gene expression levels of ~18,000 genes in 10 different brain regions from 100 subjects. We compared our results between brain regions, to cis eQTLs from blood cells, and to published genetic association results of Bipolar Disorder.
Methods: We identified cis eQTLs in brain regions using regression analysis with age, gender and diagnosis as covariates. We then tested eQTLs found in one brain region using relaxed replication p values in other brain regions, and also compared to eQTLs from lymphoblastoid cell lines (LCLs) as expression and genotypes are available for HAPMAP samples. We also filtered previously identified GWAS results for Bipolar Disorder (Sklar et al, 2011) for functional SNPs based on these eQTLs, and in particular, analyzed one brain region (3p21) in which previously identified GWAS results implicated a large region containing many potential candidate genes.
Results: Using a false discovery $q<0.05\%$, we identified 300-400 significant cis eQTLs in each brain region. Under this threshold, the eQTLs in each brain region largely did not overlap, so overall, >2000 eQTLs were identified in the 10 brain regions. This could be because most regulation is very region-specific, or because only a small subset of eQTL is identified in this experiment due to lack of power (if only a random 10% subset of all eQTLs are identified in any brain region, the overlap is expected to be only 1%). We then asked if a given eQTL is significant in one region, does it replicate in other brain regions with at least a $p<0.05$, and in the same direction. In most cases, under these relaxed conditions, eQTLs replicated. We could not identify a single case of a clearly non replicating eQTL, or an inversion of the direction of association. By contrast, of 314 eQTLs identified in LCLs, 33 were not replicated in ANY of the 10 brain regions, and hence are hypothesized to be LCL-specific. In addition, several expression eQTLs were identified in which the direction was opposite between brain and LCLs, even after very careful accounting of SNP direction. To test whether eQTLs can be used to inform results of genome-wide association studies (GWAS) of Bipolar disorder, we analyzed a region on 3p21 which had been implicated in several meta-analyses (Scott et al., 2009, Sklar et al., 2011). In this region, a large linkage disquilibrium block is associated with bipolar disorder, implicating many potential candidate genes. However, only a subset of these genes is expressed in brain, and one of the strongest overall cis eQTLs ($p<10^{-9}$–10^{-15}) maps to this region, which is in the *ITIH4* gene.
Conclusions: Although there are differences in gene expression levels, and hence an eQTL may be region-specific because the gene is only expressed in a subset of brain regions, all eQTLs replicate with a relaxed p value in all brain regions in which a given gene was expressed. Confirming results by Ding et al. (AJHG, 2010), we find no evidence of region-specific regulation, but rather, our data suggest that lack of statistical power is the primary reason for differences between similar tissues such as brain regions. Although power is also a large factor for differences between blood and brain tissues, tissue specific regulation differences do exist between these tissues. In these cases, the same transcription factor, binding to a SNP-containing site, may act as enhancer in one tissue and repressors in another. We identified a single eQTL in a Bipolar Disorder-associated region on 3p21, suggesting *ITIH4* as a candidate gene. *ITIH4*encodes the inter-alpha trypsin inhibitor heavy chain, whose involvement in Bipolar disorder is difficult to assess. However, the eQTL SNPs and the strongest bipolar associated SNPs are not in high LD, suggesting they may be different signals. However, other genes are not excluded, as nonsynonymous (code-changing) SNPs are also within the associated region, and other mechanisms such as microRNAs have not yet been investigated. In conclusion, although sample sizes are limiting our ability to detect them, eQTLs may be a powerful way to enhance and explain genetic association studies of psychiatric disorders.

This work was funded by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C.
Keywords: microarray gene expression; genetic association; GWAS; Bipolar Disorder, eQTL
Disclosure: M. Burmeister, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; V. Strumba, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications.; B. Keller, Nothing to Disclose; E. Schmidt, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; M. Flickinger, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; E. Sliwerska, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell

University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; A. Schatzberg, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; J. Barchas, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; W. Bunney, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; R. Myers, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications.; S. Watson, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; J. Li, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; L. Scott, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications.; M. Boehnke, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; H. Akil, **Part 4:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications.

T39. The Heritability of Intelligence in a Combined Sample Community Controls and People with Schizophrenia

Dwight Dickinson*, Joey Trampush, Ningping Feng, Bhaskar Kolachana, Richard Straub, Daniel R. Weinberger

NIMH, NIH, Bethesda, Maryland

Background: Human intelligence is highly heritable (Davies et al., 2011) yet the search for replicable genetic markers associated with variability in intelligence has had limited success, even with advances in analysis of genome-wide association (GWA) data (Cirulli et al, 2010). We explored this issue by examining several common intelligence phenotypes and the impact of psychiatric illness on intelligence heritability.
Methods: Recent methodology from Yang, Visscher and colleagues (2011) permits estimation of the total amount of phenotypic variance captured by common SNPs represented in the current generation of commercial genotyping arrays. We applied this method to estimate the heritability of IQ variables from Wechsler Adult Intelligence Scales (WAIS) using GWA data from Illumina arrays available from over 1500 unrelated (relatedness cutoff of 0.025) American and German individuals with and without schizophrenia.
Results: After controlling for age, sex and education, in our combined sample of 1516 participants, 63% (s.e. = 23%, p = .003) of the variance in WAIS full-scale IQ scores was captured by common SNP information across the 22 autosomal chromosomes. Fluid (i.e., performance) IQ was more heritable ($h^2 = 51\%$, s.e. = 23%, p = .01) than crystallized (i.e., verbal) IQ ($h^2 = 27\%$, s.e. = 22%, p = .1). Processing speed as measured by the digit symbol subtest was the most heritable of the individual WAIS subtests examined ($h^2 = 51\%$, s.e. = 23%, p = .01) followed by picture completion ($h^2 = 37\%$, s.e. = 23%, p = .05). Arithmetic ($h^2 = 18\%$, s.e. = 22%, p = .2) and similarities ($h^2 = 12\%$, s.e. = 26%, p = .5) showed minimal genetic association with common SNP variation in the combined sample.
Conclusions: Consistent with prior research (Davies et al., 2011), intelligence variables showed substantial, polygenic association with common genetic variants. Fluid intelligence, particularly processing speed, was more "genetic" than crystallized intelligence. Core cognitive functions as assessed by standard IQ measures appear to be differentially linked to common genetic variation which might help explain part of the challenge in finding replicable genetic markers associated with variability in intelligence.
Keywords: schizophrenia, genetics, cognitive phenotypes, genome-wide association
Disclosure: D. Dickinson, Nothing to Disclose; J. Trampush, Nothing to Disclose; N. Feng, Nothing to Disclose; B. Kolachana, Nothing to Disclose; R. Straub, Nothing to Disclose; D. Weinberger, Nothing to Disclose.

T40. Behavioral Neurogenetics: Length of CAG Repeat in Huntingtin Below Disease Threshold Predicts Motor Skill and Behavior in Children

Peggy C. Nopoulos*, Kathy Mathews, Eric Epping, Jane Paulsen

University of Iowa, Iowa City, Iowa

Background: Simple sequence repeats (SSRs) in the genome contribute to normal variation in behavioral traits, but when expanded beyond a threshold, cause neurologic disease. Hunting-

ton Disease (HD) is caused by an expansion of greater than 39 CAG repeats in the gene Huntingtin (*HTT*). However, the effects of CAG repeats on brain function below disease threshold have not been studied. The current study estimates the relationship between brain function and CAG repeat lengths below and above disease threshold in the Huntingtin gene.
Methods: Children ages 6-18 years of age who have a parent with HD were recruited. Blood or saliva was obtained from all participants and for research purposes only CAG length of the Huntingtin gene was quantified. Motor function was assessed by the Physical and Neurologic Soft Sign (PANESS) scale; behavior was quantified by parent ratings on the Pediatric Behavior Scale (PBS) and Behavior Rating Inventory of Executive Function scale (BRIEF). The sample consisted of 76 children, 38 with CAG repeat length below disease threshold and 38 with CAG repeats above threshold.
Results: Results: The relationship between CAG repeat length and motor score was 'u-shaped' with the correlation being negative below disease threshold (the higher the CAG repeat, the better the motor skill performance) and positive above disease threshold (the greater the CAG repeat, the worse the motor score). For behavior, the CAG repeat length below disease threshold was again negatively correlated (the greater the CAG repeat length, the better the behavior scores), but above disease threshold, there was no relationship with CAG.
Conclusions: CAG repeats within the range of normal variation and below disease threshold are directly related to the motor performance and behavior. These findings support the notion that this gene, and similar ones, may have been positively selected in the process of human brain evolution. In regard to disease, the findings support the notion that there is a developmental component to disease etiology with subtle abnormalities in motor function and behavior being detected decades prior to onset.
Keywords: Huntington Disease, evolution, motor function, behavior
Disclosure: P. Nopoulos, Nothing to Disclose; K. Mathews, Nothing to Disclose; E. Epping, Nothing to Disclose; J. Paulsen, Nothing to Disclose.

T41. Pharmacogenetic Moderators of Methylphenidate and Guanfacine Response in Children and Adolescents with ADHD

Erika L. Nurmi*, Karyn S. Mallya, James McGough, Sandra K. Loo, Robert M. Bilder, Fiona Whelan, James T. McCracken

UCLA, Los Angeles, California

Background: Pharmacogenetic influences may explain differential response to commonly prescribed psychiatric medications. The consideration of pharmacogenetic factors has shown clinical utility in medical specialties such as oncology, cardiovascular medicine, and pulmonology, improving patient outcomes and reducing morbidity. An expanded understanding of pharmacodynamic factors moderating response to psychiatric medications will allow rapid treatment matching, avoid morbidity, and guide the design of novel therapeutics. While methylphenidate and guanfacine are effective treatments of hyperactive and inattentive symptoms associated with ADHD, variability in individual treatment response is substantial. We sought to determine whether genetic variation in monoamine drug targets could help explain variable treatment outcomes in a randomized, double-blind, placebo-controlled trial of dexmethylphenidate (d-MPH) and guanfacine for pediatric ADHD.
Methods: Subjects were recruited for Project I of the NIMH CIDAR Translational Research to Enhance Cognitive Control (TRECC) Center at UCLA, which aims to develop treatments that specifically remediate executive function deficits as an important path to improve outcomes. Project I was designed to test the short-term efficacy of d-MPH and guanfacine combination pharmacotherapy against standard stimulant or guanfacine monotherapy on both symptom and cognitive endpoints. We further examined the contribution of genetic variation in monoamine candidates on treatment response using the standardized ADHD-Rating Scale IV (ADHD-RS) in this carefully phenotyped sample ($n = 202$). Complete common variation in dopaminergic and adrenergic drug targets was queried, including dopamine (DA) receptors D1-D5 (DRD1, DRD2, DRD3, DRD4, DRD5), alpha-2 adrenergic receptor 2A (ADRA2A), and catabolic enzymes monoamine oxidase A (MAO-A) and B (MAO-B). Known functional and previously associated variants in the DA transporter (SLC3A6), norephinephrine transporter (SLC2A6) and catabolic enzyme catechol-o-methyltransferase (COMT) were also genotyped. Variants were selected using HapMap to identify tag SNPs (tSNPs) that capture the common variability above 10% allele frequency at a minimum r^2 of 0.8. Genotyping was performed on the Life Technologies' TaqMan genotyping platform.
Results: In children receiving d-MPH, two SNPs in DRD2 and a single ADRA2A variant predicted treatment response. None of the 7 homozygotes for the minor allele of a synonymous SNP (His313His, rs6275) met responder criteria, compared to an 80% response rate in 47 common allele carriers ($p = 0.0001$). The minor (low expression) allele of the DRD2 Taq1A variant (rs1800497) was associated with an allele dosage-dependent improvement in both groups receiving d-MPH, either alone or in combination with guanfacine ($p = 0.001$). Furthermore, haplotypes defined by these 2 DRD2 SNPs showed differential effects on treatment response ($p = 0.0017$). Finally, the minor allele of an ADRA2A promoter variant (rs521674) was associated with poor d-MPH response ($p = 0.0004$). Guanfacine response was predicted by homozygosity for the minor alleles ($p < 0.0001$) of functional variants in DRD1 (rs686) and DRD2 (rs2075654).
Conclusions: Common genetic variation in dopaminergic and adrenergic receptors influenced treatment response to standard ADHD drug therapies in our dataset. These results survive correction for multiple testing (adjusted significance threshold $p < 0.002$), and many of these variants have been shown to impact gene expression in functional assays. Monoaminergic candidate genes have been previously examined and received support in small studies of treatment response, though previous studies have not comprehensively evaluated these gene loci. Our study benefits from a randomized, double-blind, placebo-controlled design, an exhaustive genetic approach, a moderate size treatment sample, repeated outcome measures, and the focus on children and adolescents. Pediatric samples may provide additional power given reduced treatment history, comorbidity (including substance use), and polypharmacy. Our results show promise for eventual personalization of ADHD treatment algorithms and warrant replication in larger samples and prospective treatment studies.
Keywords: Pharmacogenetics, ADHD, methylphenidate, guanfacine, candidate genes
Disclosure: E. Nurmi, Nothing to Disclose; K. Mallya, Nothing to Disclose; J. McGough, **Part 1:** Consultant to Alexza Pharmaceuticals and MedImmune, On the Advisory Board of Shionogi Pharma, Inc.; Shire Pharamceuticals Inc.; Noven Pharmaceuticals, **Part 4:** NeuroSigma; Supernus Pharmaceuticals, Inc.; Shionogi Pharma, Inc., ; S. Loo, Nothing to Disclose; R. Bilder, **Part 1:** Consultant for Cypress Bioscience; Johnson & Johnson; Takeda Pharmaceuticals North America, Inc.; Merck & Co., Inc.; Shire Pharamceuticals Inc., **Part 4:** Johnson & Johnson; F. Whelan, Nothing to Disclose; J. McCracken, **Part 1:** Consultant to PharmaNet, BioMarin, Novartis Pharmaceutical Corporation, Noven Pharmaceuticals, **Part 4:** Seaside Therapeutics; Roche; Shire Pharamceuticals, Inc.; Otsuka America Pharmaceuticals, Inc.

T42. Convergent Functional Genomics of Schizophrenia: From Comprehensive Understanding to Genetic Risk Prediction

Mikias Ayalew, Helen Le-Niculescu, Daniel Levey, Alan Breier, Anantha Shekhar, John Nurnberger, Mark A. Geyer, Ming Tsuang, Daniel Salomon, Nicholas Schork, Ayman Fanous, Michael C. O'Donovan, Alexander B. Niculescu*

Indiana University School of Medicine, Indianapolis, Indiana

Background: Schizophrenia is a devastating disorder affecting approximately 1% of the population. While there is clear evidence

for roles for both genes and environment, a comprehensive biological understanding of the disorder has been elusive so far. Most notably, there has been until recently a lack of concerted integration across functional and genetic studies, and across human and animal model studies, resulting in missed opportunities to see the whole picture.
Methods: We have used a translational convergent functional genomics (CFG) approach to identify and prioritize genes involved in schizophrenia, by gene-level integration of genome-wide association study (GWAS) data with other genetic and gene expression studies in humans and animal models.
Results: Using this polyevidence scoring and pathway analyses, we identify top genes (DISC1, TCF4, MBP, MOBP, NCAM1, NRCAM, NDUFV2, RAB18, as well as ADCYAP1, BDNF, CNR1, COMT, DRD2, DTNBP1, GAD1, GRIA1, GRN2B, HTR2A, NRG1, RELN, SNAP-25, TNIK), brain development, myelination, cell adhesion, glutamate receptor signaling, G-protein coupled receptor signaling and cAMP-mediated signaling as key to pathophysiology and as targets for therapeutic intervention. Overall, the data is consistent with a model of disrupted connectivity in schizophrenia, resulting from the effects of neurodevelopmental environmental stress on a background of genetic vulnerability. In addition, we show how the top candidate genes identified by CFG can be used to generate a genetic risk prediction score (GRPS) to aid schizophrenia diagnostics, with predictive ability in independent cohorts. The GRPS also differentiates classic age of onset schizophrenia from early onset and late-onset disease. We also show, in three independent cohorts, two European-American (EA) and one African-American (AA), increasing overlap, reproducibility and consistency of findings from SNPs to genes, then genes prioritized by CFG, and ultimately at the level of biological pathways and mechanisms. Lastly, we compared our top candidate genes for schizophrenia from this analysis with top candidate genes for bipolar disorder and anxiety disorders from previous CFG analyses conducted by us, as well as findings from the fields of autism and Alzheimer.
Conclusions: Overall, our work maps the genomic and biological landscape for schizophrenia, providing leads towards a better understanding of illness, diagnostics, and therapeutics. It also reveals the significant genetic overlap with other major psychiatric disorder domains, suggesting the need for improved nosology.
Keywords: schizophrenia; convergent functional genomics; pathways; genetic risk prediction; biomarkers.
Disclosure: M. Ayalew, Nothing to Disclose; H. Le-Niculescu, **Part 1:** My spouse is a founder of Mindscape Diagnostics; D. Levey, Nothing to Disclose; A. Breier, **Part 1:** Eli Lilly and Co.; A. Shekhar, Nothing to Disclose; J. Nurnberger, Nothing to Disclose; M. Geyer, Nothing to Disclose; M. Tsuang, Nothing to Disclose; D. Salomon, Nothing to Disclose; N. Schork, **Part 1:** Co-Founder, Cypher Genomics; A. Fanous, Nothing to Disclose; M. O'Donovan, Nothing to Disclose; A. Niculescu, **Part 1:** Founder, Mindscape Diagnostics

T43. Identifying Rare Variants for Obsessive-compulsive Disorder Using Family-based Whole Exome Sequencing Analysis: Preliminary Findings

Paul Arnold*, Bingbin Li, Christian Marshall, Anath Lionel, Stephen Scherer, Gregory L. Hanna

Hospital for Sick Children, Toronto, Ontario, Canada

Background: Obsessive-Compulsive Disorder (OCD) is a highly heritable and genetically heterogeneous psychiatric disorder characterized by repetitive, intrusive thoughts and compulsive behaviours. Candidate gene and genome-widelinkage and association studies suggest common genetic variants that may be implicated in the disorder. However, there are no consistently replicated variants and these studies have not comprehensively surveyed both rare and common variants in the coding region of the genome, an approach which has recently become possible with the advent of whole exome sequencing. The objective of this study is to identify coding variants associated with OCD within a single large family by combining linkage analysis and whole exome sequencing.
Methods: We examined a four-generation pedigree of 15 individuals with seven individuals affected by OCD. Single nucleotide polymorphism (SNP) data from the Illumina 610-Quad array was used for linkage analysis and to check for rare copy number variants (CNVs). Sequence capture was performed using the SureSelect Human AllExon 50 Mb kit (Agilent), followed by next-generation sequencing using the SOLiD 5500 XL system (Applied biosystems). Linkage analysis was performed using Merlin and CNV analysis using PennCNV and CNVpartition. Alignment of sequencing reads to the human genome was performed using BFAST, and variants were called using the Genome Analysis Tool Kit (GATK). We selected the two most distantly related affected individuals (a childhood-onset proband and her great-aunt) to look for shared exonic variants.
Results: Initial linkage analysis identified a linkage peak of lod = 2.3 at 9p24, a region previously linked with neuropsychiatric disorders such as schizophrenia, autism spectrum disorder and OCD. Both affected relatives displayed linkage to the 9p24 region. On whole exome sequencing, mean read depth for both individuals was 25X, with 80% of the targeted bases captured with at least 10X read depth. Across the exome, we identified over 750 rare, non-synonymous single nucleotide variants per individual that were predicted to be damaging using SIFT. We identified rare deleterious SNVs in KANK1 in the linkage region and found several damaging variants in candidate genes outside the region as well, including CNTNAP3, GRIK2, SLC1A3, NRG1, and CNTNAP5. No CNVs interrupting exons in potential candidate genes were identified.
Conclusions: Our preliminary results suggest that rare, coding variants may be associated with OCD within families. We are currently verifying these variants using Sanger sequencing, and will be conducting whole exome sequencing on more families in order to identify additional coding variants of possible etiological relevance to OCD.
Keywords: Whole exome sequencing, obsessive-compulsive disorders, rare variants, linkage analysis.
Disclosure: P. Arnold, **Part 4:** Research operating grant from DNA Genotek (2012 - 2013); B. Li, Nothing to Disclose; C. Marshall, Nothing to Disclose; A. Lionel, Nothing to Disclose; S. Scherer, **Part 1:** Paid Consultant, Scientific Advisory Board, Population Diagnostics; G. Hanna, Nothing to Disclose.

T44. *De Novo* Mutation of the Dopamine Transporter Gene Reveals a Novel Component of Autism Pathogenesis

James S. Sutcliffe*, Peter Hamilton, Kevin Erreger, Andrea Belovich, Mark J. Daly, Aurelio Galli

Vanderbilt University, Nashville, Tennessee

Background: Autism spectrum disorders (ASD) are phenotypically and etiologically complex. Genetic factors are established to contribute to ASD liability, and recent studies show that its genetic architecture comprises (1) modest numbers of genes harboring common alleles conferring small main effects on risk; (2) rare *de novo* and inherited genomic copy number variation (CNV) as a significant risk class; and (3) emerging data suggesting that rare *de novo* and inherited sequence variants contribute to risk. Overall, genetic heterogeneity is extreme with hundreds of genes harboring functional variation predicted to risk effects. To further explore the role of rare, discrete variation, the NIH ARRA Autism Sequencing Consortium sequenced the exomes of 175 parent-child trios and identified numerous functional *de novo* point mutations (DNMs). One DNM resulted in a missense substitution (T356M) in the SLC6A3 gene encoding the dopamine transporter (DAT), implicated in attention deficit-hyperactivity disorder (ADHD), a co-occurring condition in approximately 40% of people with ASD. Moreover, precedent exists for rare coding variation in SLC6A3 (A559V) that exhibits normal reuptake but anomalous efflux patterns.

Methods: To determine whether the T356M coding variant impacted DAT function we engineered *in vitro* expression construct also encoding a fluorescent tag, replacing the Thr at position 356 with the Met encoding sequence. Both wildtype (WT) and mutant constructs were analyzed in a heterologous (CHO cell) transfection system for dopamine (DA) uptake and by amperometry for DA efflux from the presynaptic terminal upon application of amphetamine, a property of the WT transporter.
Results: The DAT T356M variant displays strikingly altered functional and biophysical properties relative to WT human DAT indicating a profound effect of this *de novo* mutation. Standard experiments to measure DA uptake revealed a near absence of uptake activity for the mutant transporter compared with WT. Moreover, patch clamp experiments to electrophysiologically measure AMPH-induced DA efflux revealed a substantial reduction of efflux as seen in WT-expressing cells. To control for potential differences in protein expression and trafficking, both western blot and cell surface biotinylation analysis demonstrated that T356M transporter is actually expressed at greater levels on the cell surface, yet still unable to uptake DA and respond to normal AMPH-induced DA efflux.
Conclusions: Our studies have identified a novel ASD-associated mutation in a gene prominently implicated in other neuropsychiatric disorders based on previously isolated and characterized rare mutations. The T356M variant however presents with a starkly different molecular phenotype expected to exert a substantial impact on normal regulation of DA homeoostasis. While these results are based on a single DNM and a single pedigree, relevance to existing psychiatric conditions and relevance to routine treatment of ADHD-related behaviors (methylphenidate and amphetamine) supports the concept that this is a highly penetrant ASD risk variant. Moreover, several genes whose proteins directly interact with or have substantive roles in regulating DAT are also affected by functional point mutations. While additional studies are required, we propose that altered DA function represents a potentially important and relatively novel area of investigation for ASD pathogenesis.
Keywords: autism exome sequencing dopamine transporter *de novo* mutation dopamine
Disclosure: J. Sutcliffe, Nothing to Disclose; P. Hamilton, Nothing to Disclose; K. Erreger, Nothing to Disclose; A. Belovich, Nothing to Disclose; M. Daly, Nothing to Disclose; A. Galli, Nothing to Disclose.

T45. The Genome-wide Supported Variant MicroRNA-137 Predicts Phenotypic Heterogeneity within Schizophrenia

Tristram Lett, Mallar Chakravarty, Virginia Goncalves, Arun K. Tiwari, Daniel Felsky, Jason Lerch, Eva Brandl, Jeffrey Lieberman, Herbert Y. Meltzer, James L. Kennedy, Aristotle Voineskos*

Centre for Addiction and Mental Health, University of Toronto, Ontario, Canada

Background: MicroRNAs may be critically important genetic mechanisms contributing to phenotypic heterogeneity, a central challenge in the study of neuropsychiatric disorders. Small non-coding microRNAs function as crucial regulators of gene expression, and have been identified as potent disease modifiers. MicroRNA-137 serves as a regulator of adult neural stem cell maturation and migration and in gliogenesis.
Methods: Associations between age-at-onset in four separate samples (total $n = 510$) and MIR137 genotype (single nucleotide polymorphism, rs1625579, near the *MIR137* gene (1p21.3), with genome-wide significance for association with schizophrenia) were examined. In one of these samples ($n = 213$ subjects total), associations between MIR137 genotype and brain structure were examined, using imaging phenotypes characteristically found to be different in patients with schizophrenia compared to controls, namely lateral ventricle and hippocampal volume, cortical thickness, and white matter integrity.
Results: We demonstrate that MIR137 genotype strongly predicts age at onset of psychosis across four independent samples of patients with schizophrenia ($F_{1,540} = 21.4$, $p = 3.1x10^{-5}$). In an imaging-genetics subsample and additional matched controls ($N = 213$), patients with schizophrenia homozygous for the T risk allele had reduced white matter integrity throughout the brain ($F_{3,209} = 13.6$, $p = 3.88x10^{-8}$) as well as smaller hippocampi, and larger lateral ventricles; the brain structure of patients who were carriers of the protective G was no different from healthy control subjects for these regions.
Conclusions: Our findings suggest that *MIR137* substantially influences phenotypic variation in a manner that may direct treatment decisions, and the consequence of genetic risk factors may be distinct in schizophrenia compared to healthy controls.
Keywords: Micro-RNA, neuroimaging, genetics, schizophrenia, age-at-onset
Disclosure: T. Lett, Nothing to Disclose; M. Chakravarty, Nothing to Disclose; V. Goncalves, Nothing to Disclose; A. Tiwari, Nothing to Disclose; D. Felsky, Nothing to Disclose; J. Lerch, Nothing to Disclose; E. Brandl, Nothing to Disclose; J. Lieberman, **Part 1:** JAL reports having received research funding or is a member of the advisory board of Allon, Alkermes Bioline, GlaxoSmithKline Intracellular Therapies, Lilly, Merck, Novartis, Pfizer, Pierre Fabre, Psychogenics, F. Hoffmann-La Roche LTD, Sepracor (Sunovion) and Targacept; H. Meltzer, **Part 1:** Board Membership - Acadia, Consultancy- Sunovion Novartis, Janssen, Acadia, Teva, Lilly, Jazz Pharmaceuticals, Employment- Suregene, Expert Testimony- Janssen, Grants/Pending Grants - Sunovion Novartis, Dainippon Sumitomo, Envivo, Lilly, Payment for Lectures including Service on Speakers Bureaus - Sunovion Novartis, Patents (Pending, Planned or Issued)- Dainippon Sumitomo, Payment for Development of Educational Presentations - Teva, Stock/Stock Options- Acadia, Glaxo, Advisor/Researcher - Centerstone Research Institute; J. Kennedy, **Part 1:** JLK has been a consultant to GSK, Sanofi-Aventis, and Dainippon-Sumitomo; A. Voineskos, Nothing to Disclose.

T46. A System Level Transcriptomic Analysis in Schizophrenia Postmortem Brain

Panos Roussos*, Pavel Katsel, Kenneth L. Davis, Larry Siever, Vahram Haroutunian

Mount Sinai School of Medicine, New York, New York

Background: Schizophrenia is a common, highly heritable, neurodevelopmental mental illness, characterized by genetic heterogeneity. A systems biology approach based on weighted gene coexpression network analysis (WGCNA) was used to determine transcriptional networks in schizophrenia.
Methods: Brain tissue specimens were derived from the MSSM/VA Medical Center Brain Bank. A total number of 108 postmortem brain tissue samples (54 cases with schizophrenia; 54 controls) four different cerebrocortical regions (dorsolateral prefrontal cortex, middle temporal area gyrus, temporopolar area and anterior cingulate cortex) were analyzed using the Affymetrix U133 Plus 2.0 arrays.
Results: The oligodendrocyte, microglia, mitochondria and neuron (GABAergic and glutamatergic) related modules were associated with disease status. Genome-wide association studies in schizophrenia and other illnesses demonstrated that the neuronal (GABAergic and glutamatergic) and oligodendrocyte modules are enriched for genetically associated variants, whereas the microglial and mitochondrial modules are not, providing independent support for more direct involvement of these gene expression networks in schizophrenia. Inter-regional coexpression network analysis showed that the gene expression patterns that typically differentiate the frontal, temporal and cingulate cortices in controls diminish significantly in schizophrenia.
Conclusions: These results support the existence of convergent molecular abnormalities in schizophrenia, providing a molecular neuropathological basis for the disease.
Keywords: gene expression, human postmortem, myelin, GABA, glutamate
Disclosure: P. Roussos, Nothing to Disclose; P. Katsel, Nothing to Disclose; K. Davis, Nothing to Disclose; L. Siever, Nothing to Disclose; V. Haroutunian, Nothing to Disclose.

T47. Elevated Omega-6/Omega-3 Fatty Acid Ratio Predicts Depression Development Following Interferon-alpha Treatment: Relationship with Interleukin-6

Francis E. Lotrich*, Barry Sears, Charles Reynolds, Robert McNamara

University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Background: While converging translational evidence suggests that elevated immune-inflammatory signaling is relevant to the pathoetiology of depression, the risk factors associated with inflammation-induced depression remain poorly understood. One potential etiological mechanism is a dysregulation in polyunsaturated fatty acid (PUFA) homeostasis. Indeed, omega-3 fatty acids (eicosapentaenoic acid – EPA, 20:5n-3, docosahexaenoic acid – DHA, 22:6n-3) and omega-6 fatty acids (di-homo-gamma-linolenic acid – DGLA, 20:3n-6; arachidonic acid – AA, 20:4n-6) have opposing effects on inflammatory signaling, and cross-sectional studies have repeatedly found that patients with major depressive disorder (MDD) exhibit reductions in long-chain omega-3 (LCn-3) fatty acids and associated elevations in the AA/EPA + DHA ratio. Moreover, controlled intervention studies have found that decreasing this ratio through administration of EPA + DHA can reduce depression symptom severity in patients with MDD. The objective of the present study was to prospectively investigate whether low baseline LCn-3 fatty acid status was associated with increased risk for developing depression in response to treatment with the pro-inflammatory cytokine interferon-alpha (IFN-alpha) in hepatitis C patients. We additionally examined whether fatty acid status was associated with markers of inflammatory status, interleukin-6 (IL-6) and C-reactive protein (CRP), and the ability of IFN-alpha to successfully resolve hepatitis C infection.
Methods: Using a within-subject prospective design of 138 subjects, we examined whether baseline plasma phospholipid LCn-3 fatty acid (EPA, DHA) and omega-6 (DGLA, AA) fatty acid levels were associated with depression vulnerability in hepatitis C patients treated with IFN-alpha. Depression was assessed using the Structured Clinical Interview DSM-IV and the Montgomery-Asberg Depression Rating Scale (MADRS); and plasma IL-6 and CRP levels were determined using a high-sensitivity quantitative enzyme immunoassay.
Results: In Cox regressions, lower baseline DHA predicted depression incidence ($B = -1.3 +/- 0.6$; $p = 0.04$), as did elevated DGLA ($B = 0.53 +/- 0.23$; $p = 0.02$) and AA/EPA + DHA ratio ($B = 1.22 +/- 0.45$; $p = 0.007$). In fact, the AA/EPA + DHA ratio predicted depression after controlling for other critical variables such as sleep quality and race ($B = 1.15 +/- 0.43$). To illustrate using Kaplan-Meier, those in the upper median of AA/EPA + DHA ratios were more than 50% more likely to develop depression than those in the lower median (Mantel-Cox log rank $X2 = 5.4$; $p = 0.02$). A higher AA/EPA + DHA ratio was positively associated with treatment-emergent increases in MADRS scores ($F = 4.0$; $p < 0.05$) and IL-6 levels ($F = 107.4$; $p < 0.05$), but not C-reactive protein levels. Most of the IL-6 levels were < 1.5 ng/mL for those in the upper median of AA/EPA + DHA, compared to most having levels of > 4.5 ng/mL for those in the lower median of AA/EPA + DHA. Importantly, fatty acid status was not associated with sustained viral response to IFN-alpha treatment.
Conclusions: This prospective evidence supports the hypothesis that an elevated AA/EPA + DHA ratio increases vulnerability to depression in response to systemic inflammation, and indicates a relationship with greater IFN-induced IL-6 levels. This paradigm is therefore well-suited to prospectively evaluate primary prevention strategies, and studies are warranted to determine whether reducing the AA/EPA + DHA ratio prior to IFN-alpha treatment is protective against inflammation-induced depression.
Keywords: psychoneuroimmunology cytokines
Disclosure: F. Lotrich, Nothing to Disclose; B. Sears, **Part 1:** President of Zone Labs, Inc., Chairman of MedWell Foods, Inc., Founder of Inflammation Research Foundation (501c), **Part 2:** as above, **Part 3:** as above; C. Reynolds, **Part 1:** CFR has received pharmaceutical supplies for NIH-sponsored research from GlaxoSmithKine, Pfizer Inc, Eli Lilly and Co, Bristol Meyers Squibb, Wyeth Pharmaceuticals, and Forest Pharmaceuticals; R. McNamara, Nothing to Disclose.

T48. Low Vascular Endothelial Growth Factor and Interleukin-8 in Cerebrospinal Fluid of Suicide Attempters

Jussi Jokinen*, Josef Isung, Shahin Aeinehband, Björn Mårtensson, Peter Nordström, Fredrik Piehl, Marie Åsberg

Karolinska Institutet, Stockholm, Sweden

Background: The neurotrophic, neurogenesis hypothesis postulates that growth factor disturbances are important in the pathogenesis of neuropsychiatric disorders. A dysregulated immune system influencing pathways for cytokine regulation and growth factor expression is implicated in the pathophysiology of several neuropsychiatric disorders.
Methods: Forty three medication free suicide attempters (15 men, mean age 45 years and 28 women, mean age 36 years) admitted to the psychiatric wards at the Karolinska University Hospital were recruited to the present study. Ninety-five percent of participants had at least one current Axis I psychiatric diagnosis; 79% of patients fulfilled criteria for mood disorders. Twenty percent of the patients had a co-morbid substance related disorder (mostly alcohol dependence). Among Axis II diagnoses, 37% of the patients fulfilled criteria for a personality disorder. Depression severity was rated using the Montgomery Asberg Depression Rating Scale (Montgomery and Åsberg, 1979). Twenty healthy male volunteers (mean age 29 years) were recruited and screened with a SCID interview performed by a trained psychiatrist to exclude previous or current psychiatric problems or medical conditions. Healthy volunteers were screened for absence of psychiatric illness in the first-degree relatives. Lumbar punctures were performed at the end of the washout period in a standardized manner between 8 and 9 am after fasting in bed since midnight. CSF Samples were run on two MSD Human VEGF 96-well plates (K151BMC-1; Gaithersburg, MD) and on two MSD Human Pro-inflammatory-4 II Ultra-Sensitive 96-well plates (K15025C-1).
Results: CSF Vascular endothelial growth factor (VEGF) and CSF interleukin-8 (IL-8) levels were significantly lower in suicide attempters. Further, CSF VEGF showed a significant negative correlation with depression severity measured with the Montgomery Åsberg Depression Rating Scale (MADRS).
Conclusions: Our finding suggests that a downregulation of VEGF and IL-8 levels is implicated in the pathophysiology underlying suicidal behaviour and depression. We have previously reported that low plasma levels of VEGF were associated with suicide risk in suicide attempters.
Keywords: Cytokines, growth factors, suicide, depression, VEGF, IL 8
Disclosure: J. Jokinen, Nothing to Disclose; J. Isung, Nothing to Disclose; S. Aeinehband, Nothing to Disclose; B. Mårtensson, Nothing to Disclose; P. Nordström, Nothing to Disclose; F. Piehl, Nothing to Disclose; M. Åsberg, Nothing to Disclose.

T49. Influence of Acute Tryptophan Depletion on Attentional Performance in Adults with ADHD

Florian Daniel Zepf*, Christian Mette, Marco Grabemann, Mona Abdel-Hamid, Jennifer Uekermann, Caroline Biskup, Jens Wiltfang, Bernhard Kis

RWTH Aachen University/JARA Translational Brain Medicine, Aachen, Germany

Background: There is some preliminary evidence suggesting an involvement of the neurotransmitter serotonin (5-HT) in attention deficit hyperactivity disorder (ADHD). To date, the impact of the neurotransmitter 5-HT on different neuropsychological functions in adults with ADHD is under-investigated. In the present study we aimed to examine the effects of acute tryptophan depletion (ATD)

and the resulting reduction in central nervous system 5-HT synthesis on target/non-target discrimination ability and sustained attention in adults with ADHD using an AX-Continuous Performance Test (AX-CPT).
Methods: Twenty male patients with ADHD (age: M = 30.25 SD = 9.37) and twenty male healthy controls (age: M = 27.90 SD = 6.01) received ATD on one day and a tryptophan-balanced control condition (BAL) on another day. The study design was a double-blind within-subject crossover design. A continuous performance test (AX-CPT) with three conditions (AX, AY and BX) for assessment of attentional processes as indexed by target/non-target discrimination was administered to patients and controls on both days under depleted (ATD) and sham-depleted (BAL) conditions.
Results: When compared to controls, patients with ADHD had a significantly decreased reaction time in conditions AX and AX_E of the AX-CPT. Patients with ADHD also showed fewer correct responses in conditions AX and AY and showed a higher rate of errors (condition AX_E) independent of ATD or BAL intake. Omission errors increased in both groups after intake of ATD but not after BAL consumption.
Conclusions: The present preliminary results are indicative of the contribution of serotonergic neurotransmission to attentional processes in adults with ADHD. Future large-scale studies are needed in order to confirm these preliminary data. In addition, studies involving young people with ADHD and healthy controls assessing attentional performance are warranted in order to study the developmental trajectory of the influence of 5-HT on attentional performance.
Keywords: ADHD, tryptophan depletion, attentional performance.
Disclosure: F. Zepf, **Part 1:** Speaker honoraria, unrestricted educational grant and travel support from Shire Pharmaceuticals, **Part 2:** RWTH Aachen University/JARA Translational Brain Medicine, **Part 4:** BMWI-/ZIM KOOP grants (funded by the German Federal Ministry for Economics and Technology) with FA Dr. Kellner (Karlsruhe/Germany, 2 grants) and FA Neuroconn (Ilmenau/Germany) and FA Hasomed (Magdeburg/Germany). Unrestricted award from the American Psychiatric Association (APA), the American Psychiatric Institute for Research and Education (APIRE), and AstraZeneca (Young Minds in Psychiatry Award). Grant support from the German Society for Social Pediatrics and Adolescent Medicine, the Paul and Ursula Klein Foundation, and the Dr. August Scheidel Foundation as well as a travel stipend from the GlaxoSmithKline Foundation. Support from the Raine Foundation for Medical Research (Visiting Professorship, University of Western Australia); C. Mette, Nothing to Disclose; M. Grabemann, Nothing to Disclose; M. Abdel-Hamid, Nothing to Disclose; J. Uekermann, Nothing to Disclose; C. Biskup, Nothing to Disclose; J. Wiltfang, Nothing to Disclose; B. Kis, **Part 1:** Speaker honoraria and member of the advisory board - MEDICE Pharma GmbH & Co. KG, Speaker honoraria, travel grants and member of the advisory board - Servier Deutschland GmbH, **Part 2:** Landschaftsverband Rheinland.

T50. DHEA and DHEAS as Potential Biomarker Candidates: Investigations in Over 600 Male OEF/OIF Era Veterans

Steven T. Szabo*, Jason D. Kilts, Gillian Parke, Rajendra A. Morey, Lawrence Shampine, Jennifer Naylor, Robert M. Hamer, Christine E. Marx

Duke University, Durham, North Carolina

Background: Emerging evidence suggests that neurosteroids such as DHEA and DHEAS may be relevant to the pathophysiology and treatment of PTSD, nicotine dependence, and other CNS conditions. DHEA and DHEAS demonstrate neuroprotective and anxiolytic-like actions in rodent models, and also exhibit neurotrophic effects. In addition, DHEA and/or DHEAS alterations have been reported in patients with PTSD and in smokers. Data linking DHEAS to resilience in a military cohort exposed to severe stressors has also been reported. We thus determined DHEA and DHEAS levels in serum samples from over 600 OEF/OIF era Veterans, and examined possible associations of these neurosteroids with behavioral symptoms, smoking, and resilience.
Methods: DHEA and DHEAS levels in serum samples from 662 male Veterans enrolled in the VA Mid-Atlantic MIRECC Registry at the Durham VA site who had served in the U.S. Military since September 11, 2001 were determined by radioimmunoassay (blood draw between 10:30AM and 2:30PM). Behavioral symptoms were assessed by the Davidson Trauma Scale (DTS), the Symptom Checklist-90-R (SCL-90-R), and other rating scales. Resilience was assessed by the Connor-Davidson Resilience Scale (CD-RISC). ANCOVA analyses were conducted examining the effect of PTSD symptoms (DTS $\geqslant 40$ vs. DTS <10; criteria determined *a priori* and identical to earlier pilot investigation in 90 male Veterans, constituting an independent cohort) on DHEA and DHEAS levels, covarying for age and smoking (as DHEA and DHEAS are known to decrease with age, and appear to increase with smoking). Pearson partial correlation coefficients were also determined in Veterans for whom CD-RISC and SCL-90-R assessments were available ($n = 621$), also controlling for age and smoking status (smoker vs. non-smoker).
Results: DHEA levels were significantly lower in Veterans with DTS total scores $\geqslant 40$ ($n = 213$; consistent with PTSD) compared to Veterans with DTS total scores <10 ($n = 291$; no/minimal PTSD symptoms), controlling for age and smoking. DHEAS was non-significantly lower in Veterans with DTS total scores $\geqslant 40$ compared to Veterans with DTS total scores <10 ($p = 0.060$). DHEAS levels were positively correlated with resilience (as assessed by the CD-RISC), $r = 0.15$, $p = 0.0002$, and inversely correlated with global severity of symptoms (as assessed by the global severity index of the SCL-90-R) and with anxiety symptoms (as assessed by the anxiety subscale of the SCL-90-R); $r = -0.14$, $p = 0.0006$ and $r = -0.13$, $p = 0.0011$, respectively, controlling for age and smoking. Smokers had higher DHEA ($p = 0.0011$) and DHEAS ($p = 0.084$) levels compared to non-smokers. As anticipated, both DHEA ($p < 0.0001$) and DHEAS ($p < 0.0001$) decreased markedly with age.
Conclusions: Neurosteroids may have potential as biomarker candidates for PTSD symptoms, smoking, and resilience, and merit future investigation in larger cohorts.
Keywords: neurosteroids, post-traumatic stress disorder, depression, veteran, dehydroepiandrosterone, smoking
Disclosure: S. Szabo, Nothing to Disclose; J. Kilts, Nothing to Disclose; G. Parke , Nothing to Disclose; R. Morey, Nothing to Disclose; L. Shampine, Nothing to Disclose; J. Naylor, Nothing to Disclose; R. Hamer, **Part 1:** Company Relationship, Abbott Served on multiple DSMBs (formerly Solvay), Acadia Advised on the design of a clinical trial, Allergan Served on a DSMB, Alkermes Consultant to DSMB (start 2011-12-15), Alpharma Served on a Mock Advisory Panel (3 meetings), AstraZeneca Statistician on a UNC contract for a clinical trial, Cenerx Advised on the design and statistical analysis plan of a clinical trial, Columbia U Serve on DSMB (start 2012-01-13), Corcept Consultant in the design and analysis of multiple clinical trials, Endo Served on a mock Advisory Committee, Eli Lilly Serve on DSMBs, Enabled MD Served on an Advisory Board, Epix Advised on the design and analysis of multiple clinical trials, J & J Consulting statistician on epidemiological analyses of data from a VA database, NeuroPharmaBoost Consult on the Design of a Clinical Trial for an antidepressant: unbilled unpaid, Novartis Served on Advisory Board, Pepper-Hamilton Advised lawyers regarding a lawsuit (1 teleconference) unbilled unpaid, Pfizer Served on multiple DSMBs, PureTechVentures Consult on the design of a Clinical Trial for an antidepressant, Roche (Genentech) Served on a DSMB, SAS Institute Taught several seminars on statistics using SAS for SAS Institute, Schwartz Served on multiple DSMBs, Solvey Served on a DSMB, Sanofi-Aventis Consulted on the design of a clinical trial, Takeda Consulted on the design of a clinical trial, Winston & Strawn Expert witness in lawsuit involving Forest, Lundbeck, Sun, and Caraco, Winston & Strawn Expert witness in lawsuit involving Teva, Barr, Mylan, Eurand, Cephalon, Anesta, Wyeth Served on an Advisory Board, NeurogensX, Inc. Served on a mock FDA Advisory Committee (Nov 30, 2011), **Part 2:** I have earned more than $10,000 per year in 2012

and 2011 serving as an expert witness employed by the law firm of Winston & Strawn, **Part 3:** I have no earthly idea of who does business with ACNP but one can look at my list above and check to see who does business with ACNP, **Part 4:** I have had no grants from any pharmaceutical company; C. Marx, **Part 1:** Co-applicant/applicant, pending patents on the use of neurosteroids and derivatives in CNS disorders and for lowering cholesterol. No patents issued. No licensing in place. Unpaid scientific advisor, Sage Therapeutics.

T51. Plasma Markers of Inflammation Correlate Directly Aggression and are Elevated in Intermittent Explosive Disorder

Emil F. Coccaro*, Royce Lee, Mary Coussons-Read

University of Chicago, Chicago, Illinois

Background: A substantial body of work demonstrates connections between the brain, behavior, and immune function, and increasingly, research shows that these relationships are bidirectional in nature. Moreover, clear relationships have been demonstrated between psychological states and immune system activity which may, also, affect behavior including depression and aggression. On the whole, human and animal studies show that aggressive and hostile behavior is associated with elevations in inflammatory markers including CRP, IL-6, and soluble IL-1B receptors. To date, however, few studies have examined relationships between aggressive behaviors and inflammatory mediators associated with psychiatric disorders. The present study examined relationships between aggressive behavior and levels of the inflammatory markers interleukin-6 (IL-6), soluble interleukin-1B receptor type II (IL1BrII), and C-reactive protein (CRP) in patients diagnosed with Intermittent Explosive Disorder (IED) compared to subjects with a diagnosed Axis I and/or Axis II, disorder (Psychiatric Controls: PC), and control subjects with no evidence of any DSM-IV Axis I or II psychopathology (Healthy Controls: HC).
Methods: 201 physically healthy subjects participated in this study. All subjects were medically healthy and all Axis I and Axis II Personality Disorder diagnoses were made according to DSM-IV criteria. Plasma samples were obtained from subjects between 9 and 11 AM through venipuncture of a forearm vein. Commercially available ELISA kits (R & D Systems) were used to quantify CRP, IL-6, and IL1β receptor in the plasma.
Results: All three plasma inflammatory markers were directly correlated with a composite measure of aggression ($r = .53$, $n = 176$, $p < .001$) in all subjects. Plasma inflammatory markers were significantly higher in subjects with Intermittent Explosive Disorder compared with psychiatric or normal control subjects ($F[2,193] = 40.11$, $p < .001$). Differences in the magnitude of circulating immune markers was not due to the current or lifetime presence of any Axis I or II disorder, nor to the influence of depressive symptoms as reflected by current BDI depression scores.
Conclusions: This is the first study to examine plasma immune markers in psychiatric and control subjects that include well characterized subjects with current history of recurrent, problematic, impulsive aggression (IED). These data clearly demonstrate that plasma markers of immune function are increased in subjects with IED compared with healthy control and psychiatric control subjects. This is consistent with previous work in this area which reported a direct correlation with Aggression scores and Plasma CRP in a separate group of personality disorder subjects (Coccaro 2005) and work suggesting an association between various markers of inflammation and anger, hostility, and depression, separately and together (Suarez et al., 2002, 2003a, 2003b, 2004) including circulating C-reactive protein levels, in groups of generally normal men and women. If true, treatment with anti-inflammatory agents may be useful in aggressive individuals to: a) possibly reduce aggressive behavior in these individuals, and/or, to reduce the risk of inflammatory processes in the development of cardiovascular disease in aggressive individuals.
Keywords: Plasma, CRP, IL-1βr, IL-6, Aggression

Disclosure: E. Coccaro, **Part 1:** Scientifc Advisory Board for Azivan Pharmaceuticals, Inc.; R. Lee, **Part 1:** I have received research grants from Azivan Pharmaceuticals, Inc., **Part 4:** I have received research grants from Azivan Pharmaceuticals, Inc.; M. Coussons-Read, Nothing to Disclose.

T52. Elevated Transcript Levels for Viral Restriction Factors in Cortical Endothelial Cells in Schizophrenia

David W. Volk*, Benjamin I. Siegel, Elizabeth J. Sengupta, Jessica R. Edelson, David A. Lewis

University of Pittsburgh, Pittsburgh, Pennsylvania

Background: Elevated tissue transcript levels of immune activation markers, such as the viral restriction factor interferon-induced transmembrane protein (IFITM) which inhibits viral entry processes and replication, have been reported in the prefrontal cortex (PFC) in schizophrenia. Maternal immune activation (MIA), which elevates cytokine levels in fetal brain and is associated with higher rates of schizophrenia in offspring, has been proposed to be a pathogenetic mechanism that may lead to a sustained elevation in immunoprotective markers such as IFITM. Interestingly, MIA in mice also has deleterious effects on PFC GABA neurons, and disturbances in PFC GABA neurons have been commonly reported in schizophrenia. To investigate whether distinct alterations in viral restriction factors and GABA neurons in the prefrontal cortex may both be influenced by a shared pathogenetic event such as MIA, we 1) quantified IFITM mRNA levels in the PFC of a large cohort of schizophrenia subjects, 2) determined the cell types that express IFITM mRNA, and 3) determined if IFITM mRNA levels were inversely related to the expression of cortical GABA markers in schizophrenia.
Methods: We used a combination of quantitative PCR and *in situ* hybridization to measure IFITM mRNA levels in PFC area 9 from 57 schizophrenia subjects, each matched to one healthy comparison subject for sex and age. The mean age, postmortem interval, brain pH, RNA integrity number, and tissue storage time did not differ between subject groups. Quantitative PCR was performed using the comparative threshold cycle method with four replicate measures per target gene, and target gene expression levels were normalized using three reference genes. *In situ* hybridization was then performed using 21 subject pairs in which IFITM mRNA levels were at least 50% higher by quantitative PCR in the schizophrenia subject relative to the comparison subject and that had available tissue sections. Three tissue sections from each subject were processed using an S^{35}-labeled antisense riboprobe for IFITM mRNA and exposed to film for optical density analysis then to nuclear emulsion and stained for Nissl substance for grain counting analysis. An analysis of covariance model with subject pair as a blocking factor was used to test the effect of diagnosis on expression level for each target mRNA with storage time, brain pH, and RNA integrity number as covariates.
Results: Using quantitative PCR, we found that mean IFITM mRNA levels in PFC gray matter were markedly elevated (+ 116%) in schizophrenia subjects relative to matched healthy comparison subjects. Optical density analysis of film autoradiographs revealed IFITM mRNA levels that were 110% higher in gray matter and 85% higher in white matter of schizophrenia subjects relative to healthy subjects. Qualitative inspection of emulsion-dipped, Nissl stained tissue sections from each schizophrenia and healthy comparison subject revealed IFITM mRNA expression in endothelial cells (distinct clusters of cells with elongated nuclei) but not in neurons (larger, lighter stained nuclei) or glia cells (smaller, darker stained nuclei). Mean IFITM grain density over endothelial cells was 63% higher in schizophrenia subjects relative to healthy subjects. Finally, in schizophrenia subjects, IFITM mRNA levels were negatively correlated with levels of multiple GABA neuron-specific mRNAs including the GABA synthesizing enzyme GAD67 ($r = -0.26$, $p = .05$), neuronal subpopulation markers parvalbumin ($r = -0.33$, $p = .012$) and somatostatin ($r = -0.54$, $p < .001$), and

the GABA neuron-specific transcription factor Lhx6 ($r = -.55$, $p < .001$).
Conclusions: Given the role of IFITM in restricting the cellular entry and replication of multiple viruses, the novel finding that IFITM is localized to endothelial cells in the PFC suggests that IFITM plays an integral part in the immune protective function of the blood brain barrier in humans. Consequently, markedly elevated IFITM in blood vessels may serve to improve the immune protection function of the blood brain barrier in schizophrenia, or, alternatively, may reflect a dysfunctional blood brain barrier in the disorder. The finding that schizophrenia subjects with higher IFITM mRNA levels in endothelial cells also have greater disturbances in cortical GABA neurons suggests that these cell-type distinct pathological disturbances may be influenced by a shared upstream insult such as MIA.
Keywords: schizophrenia, immune, GABA, postmortem, prefrontal cortex
Disclosure: D. Volk, Nothing to Disclose; B. Siegel, Nothing to Disclose; E. Sengupta, Nothing to Disclose; J. Edelson, Nothing to Disclose; D. Lewis, **Part 1:** Bristol-Myers Squibb, **Part 4:** BMS Foundation, Bristol-Myers Squibb, Curridium Ltd, and Pfizer.

T53. Broader Autism Phenotype: Relationships between Maternal/paternal BAP, Parental SSRI Treatment, WB 5-HT and Child's Autism Symptoms

Tal Levin-Decanini, Nell Maltman, Guter Stephen, Edwin H. Cook, Suma Jacob*

University of Illinois at Chicago, Chicago, Illinois

Background: Subtle expression of related traits in relatives of persons with autism spectrum disorders (ASD), known as the broader autism phenotype (BAP) has been demonstrated previously. Elevated whole blood serotonin (WB 5-HT) is the most long-standing and best-replicated biological findings in ASD. Previous research has shown a relationship between whole blood serotonin levels and parental ratings of depression but those studies did not include measurement of BAP. The present study focused on the relationship between parental BAP and sex, selective serotonin reuptake inhibitor (SSRI) treatment, and the child's autism symptoms.
Methods: Subjects included 197 children with ASD, and 357 of their parents ($n = 357$). Of these parents, 25 were taking SSRIs. Proband symptoms were measured using the ADOS, ADI-R, CRI, and RBS-R domain scores. Parental BAP was measured by the Broader Autism Phenotype Questionnaire (BAPQ). In addition to total BAPQ, Aloofness, Rigidity, Pragmatic Language subscores, nine clinical expert raters identified items that measure autism-related "insistence on sameness" (IS) in order to examine those characteristics in the parent measure that may be more closely related to proband characteristics and WB 5-HT. The BAP-IS subscale was obtained by summing responses across six statements in the Rigid subscale of the BAPQ. MANCOVAs were performed to explore relationships between sex and SSRI medication use on the subscales of parent BAPQ and proband symptom scores.
Results: There were significantly different average BAPQ scores across sex and medication groups, although the effect size was modest (Wilks' $\Lambda = 0.881$, $F(12,709) = 2.897$, $p = 0.001$; $\eta^2_\rho = 0.041$). Sex and medication had significant effects on the Total score ($F(3,271) = 5.103$, $p = 0.002$; $\eta^2_\rho = 0.058$) and on Aloof ($F(3,271) = 6.015$, $p = 0.001$; $\eta^2_\rho = 0.062$), Rigid ($F(3,271) = 5.212$, $p = 0.001$; $\eta^2_\rho = 0.055$) and the subset of items related to IS ($F(3,271) = 5.103$, $p = 0.002$; $\eta^2_\rho = 0.053$). Post-hoc analyses showed mothers others taking SSRIs also had higher Total ($p = 0.021$) and Rigid subscale scores ($p = 0.026$) than those mothers not on SSRI medications. Fathers not taking SSRIs had higher Aloof and Rigid scores compared to mothers not taking SSRIs.
Conclusions: The results of this study showed that among parents not on SSRI medication, fathers score significantly higher on multiple measures of the BAPQ than mothers, namely BAP Total, Aloof and IS-related items. We did not find a relationship between parental Rigid scores and child Insistence on Sameness scores. However, we did confirm correlation of WB 5-HT between parents and children and found higher Aloof and Rigid scores in fathers compared to mothers. The increase in BAPQ scores in our subsample of mothers being treated with SSRIs was unexpected and requires careful interpretation and further study.
Keywords: Broader Autism Phenotype; whole blood serotonin; Autism; SSRIs
Disclosure: T. Levin-Decanini, Nothing to Disclose; N. Maltman, Nothing to Disclose; G. Stephen, Nothing to Disclose; E. Cook, **Part 4:** Consultation to Seaside Therapeutics - Sept 2010; S. Jacob, Nothing to Disclose.

T54. Toll Like Receptors in the Prefrontal Cortex of Depressed Suicide Victims

Ghanshyam N. Pandey*, Hooriyah S. Rizavi, Xinguo Ren, Yogesh Dwivedi

University of Illinois at Chicago, Chicago, Illinois

Background: Suggested abnormalities of immune function in depression and suicide are based in part on the observation of increased levels of pro-inflammatory cytokines in the serum and post mortem brain of depressed and suicidal patients. Other evidence of involvement of the cytokines in depression is derived from studies suggesting that administration of interferon or other cytokines induces depression in patients with chronic hepatitis C, multiple sclerosis or some forms of cancer. There is also some direct as well as indirect evidence suggesting a relationship between immune dysregulation and suicide. Increased microgliosis in the post mortem brains of those patients with affective disorders and schizophrenia who committed suicide compared to normal controls subjects has been observed. Some investigators have also found increase levels of pro-inflammatory cytokines such as IL-6 in the plasma of suicidal patients compared to normal control subjects and non-suicidal patients. That cytokines may be abnormal in the brain of suicidal victims is substantiated by findings of increased protein and mRNA expression levels of IL-1β, IL-6 and TNFα in the prefrontal cortex of teenage suicide victims compared with normal control subjects. Together these studies suggest abnormalities of immune function in depression and suicide. However, the reasons or mechanisms of this increased pro-inflammatory cytokines in the brain of the suicide victims are not clear.
Toll like receptors (TLRs) are a family of innate immune receptors. About 11 different TLRs have been identified in humans and several of them are present in human brain. Among them TLR3 and TLR 4 appear to be of interest in CNS innate immunity and also in neuronal function. TLR 3 is the only TLR present in the human neuron and both TLR 3 and 4 are associated with cognitive functions. TLR recognize multiple pathogens associated molecular patterns (PAMPS) or damaged associated molecular patterns (DAMPS). Interactions of the TLRs with PAMPS or DAMPS initiate signaling cascade through or independent of MYD88 and activate NF-kappa B which causes the production of cytokines and chemokines. It is thus possible that increased levels of cytokines observed in the brain of suicide victims may be related to an abnormality of TLRs. To test this hypothesis we studied the protein and gene expression of TLR3, TLR4 in the prefrontal cortex (PFC) (BA-9 region) of depressed suicide victims and matched normal control subjects.
Methods: The post mortem brain samples were obtained from the brain collection at the MarylandPsychiatryResearchCenter, Baltimore, Maryland. Samples were obtained from 24 normal control subjects and 24 depressed suicide subjects. Psychological autopsy was performed and the subjects were diagnosed according to the DSM-IV (SCID). Protein expression of TLR3 and TLR4 were determined using the western blot technique and the mRNA expression of TLR 3 and TLR4 were determined using qPCR. Statistical analysis was performed using t test and fixed effect model taking into account the effect of age, sex and PMI.

Results: We found that the protein expression levels of TLR 3 and TLR4 determined by western blot, was significantly higher in the PFC of 24 depressed suicide victims as compared to 24 normal control subjects. Similar to the protein expression we also found that the mRNA expression of TLR3 and TLR4 was significantly increased in the PFC of depressed suicide victims as compared to normal control subjects. There was no significance difference in the age, PMI or brain pH between normal control subjects and depressed suicide victims.
Conclusions: This study shows that the protein and mRNA expression of both TLR3 and TLR4 are increased in the PFC of depressed suicide victims suggesting that suicidal behavior may be associated with the abnormality of innate immunity. The observed increases in the pro-inflammatory cytokines in the brain of the suicide victims may be related to an increase of the TLR receptors, as activation of the TLR receptors causes the production of cytokines and chemokines through a signaling mechanism mediated through or independent of MYD88 and activate NF-kappa B. Both TLR3 and TLR4 have been implicated in the pathogenesis of cognitive impairment as well as AD. TLR3 is the only TLR present in the human neuron and has significant effects on cognitive performance of mice in hippocampal dependent and independent tasks. These finding suggest that both TLR3 and TLR 4 which are involved in the cognitive functions may play an important role in the patho-physiology of depression and suicide and that increase levels of pro-inflammatory cytokines in the brain may be related to an increase in TLRs. Supported by NIMH RO1 MH 048153 and RO1- MH098554 (GNP).
Keywords: Toll like receptors, Suicide, Cytokines, Depression, post mortem brain
Disclosure: G. Pandey, Nothing to Disclose; H. S. Rizavi, Nothing to Disclose; X. Ren, Nothing to Disclose; Y. Dwivedi, Nothing to Disclose.

T55. Reduced μ-opioid Response to Social Rejection in Major Depressive Disorder

David T. Hsu*, Benjamin J. Sanford, Kortni K. Meyers, Kathleen E. Hazlett, Brian J. Mickey, Scott A. Langenecker, Jon-Kar Zubieta

University of Michigan, Ann Arbor, Michigan

Background: Social rejection, i.e., being excluded or not liked by others, has powerful effects on cognitive-emotional states and is strongly associated with major depressive disorder (MDD). The μ-opioid receptor (MOR) system, which has a prominent role in reducing physical pain, may also regulate the emotional "pain" of social rejection. We sought to examine the MOR response to social rejection in MDD patients compared to healthy controls.
Methods: Participants were 13 medication-free patients with current MDD (9 females, 4 males; mean age ± *SD*, 29 ± 11 years) and 18 healthy controls (13 females, 5 males; mean age ± *SD*, 32 ± 12 years). MDD patients were diagnosed by structured clinical interview, scored >14 (mean score ± *SD*, 20 ± 5) on the 17-item Hamilton Depression Rating Scale, and were free of antidepressant medication for at least six months at the time of the study. Subjects rated online profiles of preferred-sex individuals with whom they would most like to form an intimate relationship. A few days later they were given feedback that they were not liked by 12 of their highest-rated profiles during positron emission tomography (PET) with intravenous administration of the selective MOR radiotracer [^{11}C]carfentanil. Control blocks contained a visual presentation similar to rejection blocks but with no feedback. Block order was randomized and counterbalanced across participants. *A priori* volumes of interest for analysis included the amygdala, ventral striatum, thalamus, dorsal anterior cingulate, anterior insula, and periaqueductal gray, which are rich in MORs. Self-completed questionnaires including the trait measure Ego Resiliency and state measures of Hurt Feelings (items: hurt, pained, injured, and wounded) were given before and during the scan, respectively.
Results: MDD patients reported higher levels of Hurt Feelings immediately after the rejection block compared to healthy controls (rejection-baselinesubtraction scores, $t_{27} = 3.70$, $P = 0.001$). Compared to healthy controls, patients with MDD showed lesser MOR activation during rejection compared to baseline blocks in the right amygdala ($t_{29} = 5.00$, $P = 0.00001$), right ventral striatum ($t_{29} = 4.66$, $P = 0.00003$), and midline thalamus ($t_{29} = 3.73$, $P = 0.0004$). As expected, Ego Resiliency was lower in MDD patients compared to healthy controls ($t_{29} = 6.08$, $P = 0.000001$). Planned follow-up analyses showed that in MDD patients, Ego Resiliency was not significantly correlated with MOR activation. In contrast, in healthy controls this trait was significantly correlated with activation in the right amygdala ($r = 0.62$, $P = 0.006$) and right ventral striatum ($r = 0.48$, $P = 0.04$).
Conclusions: These results demonstrate a reduced endogenous MOR response to social rejection in MDD patients compared to healthy controls. These differences were found in the amygdala, ventral striatum, and midline thalamus. Activation of the MOR system in brain pathways regulating mood and motivation may facilitate recovery from the emotional pain of social rejection, in parallel to its role in reducing physical pain and social separation distress in several nonhuman species. In MDD patients, reduced MOR responses in these regions may hinder the ability to recover from the negative effects of social rejection. Furthermore, in healthy controls but not MDD patients the magnitude of MOR activation depended on one's predisposition for resiliency, suggesting that a responsive MOR system to social rejection contributes to resiliency.
Keywords: social rejection opioid depression resiliency
Disclosure: D. Hsu, Nothing to Disclose; B. Sanford, Nothing to Disclose; K. Meyers, Nothing to Disclose; K. Hazlett, Nothing to Disclose; B. Mickey, **Part 3:** Dr. Mickey received salary support from St. Jude Medical for research unrelated to this abstract; S. Langenecker, Nothing to Disclose; J. Zubieta, Nothing to Disclose.

T56. Neurochemical Effects of Ketamine Administration in Healthy Humans: An MRS Time-course Study

Lawrence S. Kegeles*, Xiangling Mao, Najate Ojeil, Raffael Massuda, Mariana Pedrini , Chi-Ming Chen, Anissa Abi-Dargham, Mark Slifstein, Matthew Milak, Carolyn I. Rodriguez, Dikoma C. Shungu

Columbia University, New York, New York

Background: The effects on the brain of acute administration of ketamine are of current interest because of its known psychotogenic [1, 2] and antidepressant [3, 4] properties. Early rodent microdialysis studies [5] showed a surge in medial prefrontal cortex (MPFC) glutamate (Glu), and recent rodent studies of molecular mechanisms have suggested that this surge is a key step in downstream synaptogenesis and antidepressant action [6]. Magnetic resonance spectroscopy (MRS) studies in humans of the MPFC and other brain regions have been reported [7-10]. These studies have examined one or two time points and have in some but not all cases documented a ketamine-induced increase in glutamatergic compounds. Our goal was to study the time course of the response of glutamate-glutamine (Glx) and GABA levels to acute ketamine administration in healthy human subjects.
Methods: We studied 12 healthy volunteers (7 female, ages 28 ± 6 y) who were given a constant i.v. infusion of ketamine 0.5 mg/kg over 40 min during an MRS study of Glx and GABA in the MPFC using a 3T GE system and a J-edited PRESS sequence. Both neurochemicals were normalized to the internal water signal of the MPFC voxel. Six sequential acquisitions each of 15 min duration (90 min total) were obtained before, during, and following the infusion. Subjects were rated with Profile of Mood States (POMS), Clinician-Administered Dissociative States Scale (CADSS), and Brief Psychiatric Rating Scale (BPRS) before and after scanning.
Results: After the start of ketamine infusion, both Glx/W and GABA/W increased to a maximum in the third (15-30 min post initiation of infusion) acquisition and returned to baseline levels by the end of the study. Maximum increases were more marked for Glx (to 117% ± 25% of baseline) than for GABA (to 111% ± 24% of baseline), and changes were significant by repeated measures

ANOVA ($p = .02$ for Glx; $p = .04$ for GABA), while a more conservative linear mixed model gave $p = .03$ for Glx and $p > .05$ for GABA. Rating scales showed significant increases in POMS ($P = .01$) and CADSS ($P < .001$) but not BPRS ratings.
Conclusions: These data constitute the first dynamical study of neurochemical effects of ketamine in healthy humans. They represent the first suggestion of a GABA surge in these subjects concurrent with the Glx surge. These data 1) suggest that prior mixed findings on ketamine effects on the glutamate system in human subjects can be understood in terms of region and time dependence of these effects; 2) are consistent with the time course of the surge in extracellular glutamate seen in rodent studies [5]. However, since MRS cannot distinguish neurochemical compartments, but instead provides total tissue neurochemical levels, they suggest that ketamine induces acute surges in net Glx and GABA synthesis of the magnitudes reported here; 3) show a remarkable correspondence to baseline neurochemical abnormalities seen in unmedicated patients with schizophrenia, who show elevated Glx/W and GABA/W in the same brain region [11], consistent with the NMDA receptor hypofunction hypothesis of schizophrenia; 4) are qualitatively similar to data acquired by our group in depressed patients [12], supporting the extrapolation from rodent studies to depressed human subjects of the possible role of the glutamate surge in the antidepressant action of ketamine; and 5) by showing elevations rather than reductions in GABA/W, suggest that the idea that GABAergic interneurons disinhibit pyramidal cells as a mechanism for the acute NMDA receptor blockade-induced glutamate surge may need refinement. Financial support: NARSAD; NCATS/NIH UL1 TR000040 [1] Domino EF et al., *Clin Pharmacol Ther* 1965;**6**:279-291. [2] Krystal JH et al., *Arch Gen Psychiatry* 1994;**51**(3):199-214. [3] Berman RM et al., *Biol Psychiatry* 2000;**47**(4):351-354. [4] Zarate CA Jr et al., *Arch Gen Psychiatry* 2006;**63**(8):856-864. [5] Moghaddam B et al., *J Neurosci* 1997;**17**(8):2921-2927. [6] Li N et al., *Science* 2010;**329**(5994):959-964. [7] Rowland LM et al., *Am J Psychiatry* 2005;**162**(2):394-396. [8] Valentine GW et al., *Psychiatry Res* 2011;**191**(2):122-127. [9] Taylor MJ et al., *J Psychopharmacol* 2012;**26**(5):733-737. [10] Stone JM et al., *Mol Psychiatry* 2012;**17**(7):664-665. [11] Kegeles LS et al., *Arch Gen Psychiatry* 2012;**69**(5):449-459. [12] Shungu DC et al., *Proc Intl Soc Mag Reson Med* 2011;**19**:4346.
Keywords: Ketamine, glutamate, GABA, MRS, schizophrenia
Disclosure: L. Kegeles, **Part 1:** Research grants, Pfizer and Amgen, **Part 4:** Research grants, Pfizer and Amgen; X. Mao, Nothing to Disclose; N. Ojeil, Nothing to Disclose; R. Massuda, Nothing to Disclose; M. Pedrini, Nothing to Disclose; C. Chen, Nothing to Disclose; A. Abi-Dargham, **Part 1:** Research support from GlaxoSmithKline, consultant for Bohringer-Engelheim, consultant and speaker for Bristol-Myers Squibb Otsuka, **Part 4:** Research support from GlaxoSmithKline; M. Slifstein, **Part 1:** Consultant for GlaxoSmithKline and Amgen and research support from Pierre-Fabre, **Part 4:** Research support from Pierre-Fabre; M. Milak, Nothing to Disclose; C. Rodriguez, Nothing to Disclose; D. Shungu, **Part 1:** Consulting fees from Roche Product Limited and from Adventist Health System/Sunbelt, Inc., d.b.a. Florida Hospital.

T57. Effects of 4 mg Pioglitazone on Mnemonic Hippocampal Function: A Pharmacologic BOLD fMRI Study in Healthy Elderly Adults

Ahmad Hariri*, Annchen Knodt, Adam Gorka, James Burke, Kathleen Welsh-Bohmer, Brenda Plassman, Daniel Burns, Stephen Brannan, Michael Kukulka, Allen Roses

Duke University, Durham, North Carolina

Background: A recent genetic association study (Roses et al., *Pharmacogenomics J.* 2010) has reinvigorated interest in dysfunction of pathways regulating mitochondrial energy metabolism in Alzheimer's disease (AD). Consequently, pharmacologic targeting of mitochondrial dysfunction as a novel therapeutic avenue in AD is being pursued. Here, we report on a preliminary pharmacologic blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) study evaluating the impact of low-dose pioglitazone, which affects mitochondrial membrane transport processes, on episodic memory-related hippocampal function in healthy elderly volunteers. We focus on memory-related hippocampal function because it is clearly linked with pathophysiology in AD (Vounou et al., *NeuroImag*e 2012), has been associated with genetic variants conferring susceptibility to AD (Wang et al., *J. Neurochem.* 2009), and is dependent on energy metabolism supported by mitochondrial function (de la Torre, *Neurodegener Dis.* 2008).
Methods: Twelve healthy elderly volunteers (2 men; mean age $= 68.8 \pm 6.6$ years) completed a within-subject pharmacologic BOLD fMRI paradigm targeting episodic memory-related hippocampal activation (Zeineh et al., *Science* 2003). Each participant underwent a baseline scan and then received their first dose of 4 mg pioglitazone as an oral solution. Daily treatment with 4 mg doses was continued for 14 days. Additional scans were completed at 7 and 14 days post baseline. Our fMRI paradigm consisted of the encoding and subsequent recall of novel face-name pairs. A distractor task (odd/even number identification) was interleaved between encoding and recall blocks to prevent maintenance of information in working memory. Three versions of the paradigm with non-overlapping face-name pairs were utilized for each subject in a pseudorandomized order. BOLD fMRI data were analyzed using random effects analyses accounting for both within- and between-subject effects using Statistical Parametric Mapping software version 8 (SPM8). Based on prior research using this paradigm, our analyses targeted BOLD effects in the left hippocampus during encoding.
Results: Repeated measures ANOVA controlling for age and gender revealed a significant main effect of treatment on left hippocampal BOLD signal during encoding ($F = 9.79$, $p = 0.0013$; cluster size $= 15$ voxels, MNI coordinates for max voxel of cluster: $x = -30$, $y = -40$, $z = 0$). *Post hoc t*-tests indicated that left hippocampal BOLD signal was significantly greater at day 14 than at baseline ($t = 2.73$, $p < 0.05$) and day 7 ($t = 4.00$, $P < 0.005$). There was no significant difference between baseline and day 7 ($t = 1.77$, $p > 0.1$). There were no significant effects of treatment on accuracy or reaction time (all p's > 0.1).
Conclusions: These findings indicate that treatment with low-dose pioglitazone is associated with increased memory-related hippocampal function. The identification of treatment effects at the level of brain mechanisms supporting behavior highlights the potential value of pharmacologic BOLD fMRI in guiding clinical decision making including dose selection. Although these effects were not manifest at the level of task performance in our sample of healthy elderly adults, such potentiation of neural function may support maintenance and, possibly, improvement of memory in at-risk individuals, including those possessing genetic variants conferring susceptibility for AD.
Keywords: Alzheimer's disease, memory, hippocampus, fMRI, pioglitazone
Disclosure: A. Hariri, **Part 1:** I received a consultant payment from Zinfandel Pharmaceuticals, Inc. in 2010, I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University, **Part 2:** I received a consultant payment from Zinfandel Pharmaceuticals, Inc. in 2010, I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University, **Part 3:** I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University, **Part 4:** The study presented in the abstract is supported by Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University; A. Knodt, Nothing to Disclose; A. Gorka, Nothing to Disclose; J. Burke, **Part 1:** I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke Univeristy, **Part 2:** I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the

company and Duke Univeristy, **Part 3:** I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke Univeristy, **Part 4:** The study presented in the abstract is supported by Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University; K. Welsh-Bohmer, **Part 1:** I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke Univeristy, **Part 2:** I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke Univeristy, **Part 3:** I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke Univeristy, **Part 4:** The study presented in the abstract is supported by Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University; B. Plassman, **Part 1:** I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke Univeristy, **Part 2:** I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke Univeristy, **Part 3:** I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke Univeristy, **Part 4:** The study presented in the abstract is supported by Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University; D. Burns, **Part 1:** I am a full-time employee of Zinfandel Pharmaceuticals, Inc., **Part 2:** I am a full-time employee of Zinfandel Pharmaceuticals, Inc., **Part 3:** I am a full-time employee of Zinfandel Pharmaceuticals, Inc., **Part 4:** The study presented in the abstract is supported by Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University; S. Brannan, **Part 1:** I am a full-time employee of Takeda Pharmaceutical Comany Limited, **Part 2:** I am a full-time employee of Takeda Pharmaceutical Comany Limited, **Part 3:** I am a full-time employee of Takeda Pharmaceutical Comany Limited, **Part 4:** The study presented in the abstract is supported by Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University; M. Kukulka, **Part 1:** I am a full-time employee of Takeda Pharmaceutical Comany Limited, **Part 2:** I am a full-time employee of Takeda Pharmaceutical Comany Limited, **Part 3:** I am a full-time employee of Takeda Pharmaceutical Comany Limited, **Part 4:** The study presented in the abstract is supported by Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University; A. Roses, **Part 1:** I am a full-time employee of Zinfandel Pharmaceuticals, Inc., **Part 2:** I am a full-time employee of Zinfandel Pharmaceuticals, Inc., **Part 3:** I am a full-time employee of Zinfandel Pharmaceuticals, Inc., **Part 4:** The study presented in the abstract is supported by Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University.

T58. Circadian Clock Gene Expression Rhythms in Cells from Patients with Bipolar Disorder Differ in Response to Lithium

Michael J. McCarthy*, Hongbing Wei, Ryan Darvish, Donna McPhie, Bruce Cohen, David Welsh

VA San Diego Healthcare System & University of California San Diego, San Diego, California

Background: Bipolar disorder is associated with abnormal sleep and activity cycles, leading to the hypothesis that the illness is related to dysfunction in the circadian clock. The circadian clock is comprised of a network of "clock genes" including *PER2* that regulate rhythms through interlocking transcription-translation loops. Supporting the assertion that the clock is altered in bipolar disorder, the mood stabilizer lithium corrects illness related activity disturbances and affects clock gene expression and rhythmic behaviors in humans and animals. Peripheral cells maintain functional molecular clocks that are similar to those within the brain, making the circadian clock amenable to study in cells from patients. However, previous measurements of clock gene expression in cells from bipolar patients have been limited by short duration and sparse sampling, factors that could make measurements over the circadian time scale imprecise. Using a luciferase reporter, we measured rhythms of clock gene expression longitudinally in cells from bipolar disorder patients and the effects of lithium on these rhythms.
Methods: Skin fibroblasts obtained from subjects with bipolar disorder (N = 19) or healthy controls (N = 19) were cultured to confluence. Cells were infected with lentiviral *Per2::luc*, a bioluminescent reporter gene that is expressed rhythmically under the control of the circadian clock. Gene expression rhythms were measured in a luminometer for 5 days in cells that were either untreated or treated with varying levels of lithium (1 mM, 10 mM) continuously for 7 days. For each cell line and drug condition, rhythm parameters (period, amplitude, phase, damping, and goodness of fit) were then established and compared between cases and controls under lithium treated and untreated conditions. A case-case analysis was conducted between subjects with differing clinical features of bipolar disorder to search for rhythm differences associated with dysphoric mania, co-morbid substance use, family history, and suicidal behaviors.
Results: In untreated cells, rhythm parameters did not differ significantly between bipolar cases and controls. In all cell lines, lithium affected *Per2::luc* expression rhythms at both drug concentrations. However, after lithium treatment, the magnitude of change in rhythm parameters differed in bipolar cases and controls. At low concentration (1 mM), lithium increased the amplitude of rhythms in controls, but failed to do so in bipolar cases. At high concentration (10 mM), lithium reduced rhythm amplitude equally in cases and controls, and lengthened rhythm periods. The magnitude of period lengthening was greater in controls compared to bipolar cases. Case-case analyses revealed modest correlations between some clinical features and individual rhythm parameters but should be regarded as preliminary due to small sample size.
Conclusions: In fibroblasts, there are no overall group differences in circadian rhythm parameters between bipolar cases and controls. However, the circadian clock in patients with bipolar disorder may respond distinctly to external factors that can regulate the clock, including drugs like lithium.
Keywords: Bipolar Disorder, Circadian Rhythms, Lithium, Fibroblast, Clock Genes
Disclosure: M. McCarthy, Nothing to Disclose; H. Wei, Nothing to Disclose; R. Darvish, Nothing to Disclose; D. McPhie, Nothing to Disclose; B. Cohen, Nothing to Disclose; D. Welsh, Nothing to Disclose.

T59. Adjunctive Treatment with Asenapine Augments the Escitalopram-induced Effects on Monoaminergic and Glutamatergic NMDA as Well as AMPA Receptor-mediated Transmission in the Medial Prefrontal Cortex

Monica M. Marcus*, Olivia Frånberg, Carl Björkholm, Anna Malmerfelt, Kent Jardemark, Torgny H. Svensson

Karolinska Institutet, Stockholm, Sweden

Background: Substantial clinical experience support the adjunctive use of low to moderate doses of atypical antipsychotic drugs (APDs) to rapidly enhance the efficacy of selective serotonin re-uptake inhibitors (SSRIs) in treatment-resistant major depressive disorder (MDD; Green MF 1996, Am J Psychiatry 153:321-330; Nelson and Papakostas 2009, Am J Psychiatry 166:908-91). Moreover, this clinical augmentation has been suggested to be at least partly

explained by an increased catecholamine outflow in prefrontal cortical areas of the brain, which has been observed in rats when combining certain atypical APDs and SSRIs (Zhang et al. 2000, Neuropsychopharmacol 23:250-62; Marcus et al. 2010, Neuropsychopharmacol 35:1952-61; Marcus et al. 2012, Synapse 66:277-90). In addition, an associated facilitation of NMDA receptor-mediated glutamatergic transmission in the medial prefrontal cortex (mPFC) of the rat has been observed. However, the rapid onset of the potent antidepressant action of both ketamine and scopolamine has been shown in rats to be initiated through facilitation of glutamatergic AMPA receptor-mediated transmission in the mPFC (Li et al. 2010, Science 329:959-64; Duman R, ACNP 2011). Asenapine is an atypical APD approved for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder (FDA, 2009; EMA, 2010). The SSRI escitalopram, the S-enantiomer of citalopram, has been shown to provide an advantageous clinical effect as well as a high tolerability compared with other SSRIs (Montgomery et al. 2007, Int Clin Psychopharmacol 22:323–29), although its antidepressant efficacy is still by no means optimal. Here we examined, in the rat, the effects of combined administration of asenapine and escitalopram on the dopamine, noradrenaline and serotonin outflow in the mPFC and the dopamine outflow in nucleus accumbens (NAc), as well as on glutamatergic NMDA and AMPA receptor-mediated transmission, respectively, in the mPFC.

Methods: We used *in vivo* microdialysis in freely moving animals to measure neurotransmitter efflux in the mPFC and the nucleus accumbens (NAc), and *in vitro* intracellular electrophysiological recordings in pyramidal cells to examine the effect on NMDA and AMPA receptor-mediated transmission in the mPFC.

Results: Adjunct treatment with low doses of asenapine (0.05 and 0.1 mg/kg s.c.) in combination with escitalopram (5 mg/kg s.c.) generated a marked enhancement of dopamine, noradrenaline and serotonin release in the mPFC as well as, to some extent, dopamine outflow in the NAc. Moreover, the combination of asenapine and escitalopram in low concentrations (1 nM and 3 nM, respectively), which had no effects when given alone, was found to facilitate both NMDA- and AMPA-induced currents in pyramidal cells of the mPFC. Furthermore, the enhanced effect on NMDA-induced currents was blocked by the D_1 receptor antagonist SCH23390.

Conclusions: Our data generally support the notion that the augmentation of SSRIs by atypical APDs in treatment-resistant MDD may be related to enhanced catecholamine output in prefrontal cortical areas, which at least should serve to enhance certain aspects of the cognitive impairment. Accordingly, the present results suggest that also asenapine may be clinically used to achieve this end, a conclusion furthermore supported by the concomitant enhancement of prefrontal NMDA receptor-mediated transmission, which is known to be involved in the control of working memory. The effect on NMDA receptor-mediated transmission was shown to be mediated via D_1 receptors, that likewise are critically involved with control of cognition. Our observation that this drug combination, just like the rapidly acting antidepressants ketamine and scopolamine, also facilitate AMPA receptor-induced responses in the mPFC, may specifically contribute to explain the rapid onset of the enhanced antidepressant effect of SSRIs, which may be generated even within a few days by adjunctive treatment with atypical APDs and provides novel experimental support for the utility of add on asenapine in treatment-resistant MDD.

Keywords: SSRI, antipsychotic, dopamine, glutamate, treatment-resistant MDD

Disclosure: M. Marcus, Nothing to Disclose; O. Frånberg, Nothing to Disclose; C. Björkholm, Nothing to Disclose; A. Malmerfelt, Nothing to Disclose; K. Jardemark, Nothing to Disclose; T. Svensson, **Part 3:** AstraZeneca and Lundbeck scientific advisory board meetings, **Part 4:** AstraZeneca, Organon, Schering-Plough, Merck, Johnson & Johnson.

T60. The Functional Significance of Antipsychotic-related Cortical Thinning in First Episode Schizophrenia

Tyler A. Lesh*, Costin Tanase, Tara Niendam, Jong Yoon, J Daniel Ragland, Michael Minzenberg, Marjorie Solomon, Cameron Carter

UC Davis, Sacramento, California

Background: Findings of structural and functional brain abnormalities are consistently replicated in magnetic resonance imaging (MRI) studies of patients with schizophrenia. Studies using voxel-based morphometry and measurements of cortical thickness identify gray matter reductions and cortical thinning in prefrontal and temporal structures, as well as increased volume in the basal ganglia. Schizophrenia patients typically show altered activation of these same regions, particularly reduced activity in dorsolateral prefrontal cortex, during fMRI tasks tapping the fronto-parietal cognitive control circuit (e.g., AX-CPT, N-back). However, the degree to which antipsychotic medications are associated with changes in brain structure, function, and behavioral performance within the illness are poorly understood. We sought to examine these effects in first episode schizophrenia patients, who were evaluated within one year of illness onset, utilizing cortical thickness measurements and fMRI. Cortical thickness measurements were derived from surface-based registration methods where homologous regions are matched, as opposed to relying upon spatial smoothing of VBM analyses, potentially offering increased sensitivity to subtle cytoarchitectural changes. The AX-CPT was used as a measure of functional fronto-parietal recruitment. When compared to healthy controls, we hypothesized that patients with schizophrenia would show thinner cortex and reduced activation of dorsolateral prefrontal cortex, as well as lower performance reflecting impaired cognitive control. Additionally, we anticipated that patients receiving antipsychotic medication compared to those who were unmedicated would show more extensive prefrontal cortical thinning in the context of improved functional activity and better behavioral performance.

Methods: Medicated ($n = 24$) and unmedicated ($n = 21$) first episode schizophrenia patients as well as healthy control participants ($n = 28$) were identified from referrals to the UC Davis Early Detection and Preventative Treatment clinic using the Structured Clinical Interview for DSM-IV. Images were obtained on a 1.5-Tesla General Electric scanner and processed using Freesurfer 4.1 (structural analysis) and SPM8 (fMRI analysis). Statistical analyses of structural data were conducted using a vertex-wide threshold of $p < .01$ followed by a cluster-wise correction for multiple comparisons (5000 Monte Carlo simulations, $p < 0.05$). Statistical analysis of AX-CPT fMRI data focused on CueB versus CueA trials and both whole-brain cluster-corrected and DLPFC region of interest analyses were performed.

Results: Analyses of structural data revealed significant cortical thinning in medicated patients with schizophrenia relative to healthy controls in dorsolateral prefrontal and orbitofrontal cortices. Unmedicated schizophrenia patients demonstrated no significant cortical thickness differences from healthy controls after cluster-wise correction. A comparison of medicated and unmedicated patients revealed significant cortical thinning in medicated patients only in the DLPFC. With regard to brain activation during the AX-CPT, both patient groups showed reduced activity in frontal and parietal regions compared to healthy controls. However, medicated schizophrenia patients also demonstrated higher DLPFC activation compared to unmedicated patients. A similar pattern emerged in behavioral performance, in which medicated patients showed higher performance (as indexed by d'-context scores) than unmedicated patients.

Conclusions: These findings highlight the complex relationship between antipsychotic treatment and the structural, functional, and behavioral deficits repeatedly identified in schizophrenia. Although treatment with antipsychotic medications was associated with prefrontal cortical thinning, treatment was also related to better cognitive control and increased prefrontal functional

activity that was comparable to healthy controls. This study also highlights the critical importance of multi-modal analyses in understanding the complex nature of structural and functional neurophysiological changes in the disorder.
Keywords: schizophrenia cognition fmri cortical thickness
Disclosure: T. Lesh, Nothing to Disclose; C. Tanase, Nothing to Disclose; T. Niendam, Nothing to Disclose; J. Yoon, Nothing to Disclose; J. Ragland, Nothing to Disclose; M. Minzenberg, Nothing to Disclose; M. Solomon, Nothing to Disclose; C. Carter, Nothing to Disclose.

T61. GR-independent Corticosterone-dopamine Interactions in the Nucleus Accumbens Mediate the Stress-induced Potentiation of Cocaine Seeking in Rats

Paul J. Gasser, Evan N. Graf, David A. Baker, Jayme McReynolds, Jonathan Hill, Amanda Ebben, Chung-Lung Chan, Mykel Robble, Oliver Vranjkovic, Daniel S. Wheeler, Robert A. Wheeler, John R. Mantsch*

Marquette University, Milwaukee, Wisconsin

Background: Although stress plays a critical role in relapse, recent studies suggest that, in many cases, rather than directly triggering cocaine use, stress may function as a "stage setter" such that stimuli that do not normally evoke relapse under stress-free conditions may precipitate use when exposure occurs in the context of stress. The goals of this study were to establish a behavioral model for examining this role of stress in drug relapse and to use the model to identify potential neurobiological mechanisms that contribute to the stage setting effects of stress on cocaine-seeking behavior.
Methods: Adult male Sprague Dawley rats were implanted with intravenous catheters and trained to self-administer cocaine (0.5 mg/kg/200 µl infusion) by pressing a lever under a fixed-ratio one schedule of reinforcement during daily 2-hr sessions. After 14 days of self-administration training, responding was extinguished by replacing the cocaine solution with saline during daily 2-hr sessions until extinction criteria were met (<10 active responses/session across 3 sessions) at which time reinstatement testing was conducted. The ability of stimuli (stress, corticosterone, etc…) to potentiate cocaine-induced reinstatement was examined by testing for reinstatement by these stimuli alone or in combination with a low, subthreshold cocaine dose (2.5 mg/kg, ip) that alone failed to evoke cocaine seeking. Initially rats were tested for the ability of a stressor -a 15-min period of intermittent electric footshock [0.5 mA, 0.5 s duration, mean inter-shock interval = 40 s (range 10-70 s)] delivered in the experimental chambers – to potentiate cocaine-induced reinstatement. Subsequently, the effects of various manipulations designed to reproduce or block the footshock-induced potentiation of reinstatement were examined.
Results: In rats with a history of daily 2 hr/day cocaine self-administration, footshock stress alone did not reinstate cocaine seeking, but rather potentiated reinstatement in response to a low cocaine dose (2.5 mg/kg, ip) that failed to reinstate cocaine seeking under control conditions (n = 7). Surgical adrenalectomy along with diurnal corticosterone replacement prevented this effect of footshock (n = 6), and the shock-induced potentiation was reproduced in non-stressed animals by administration of a physiologically relevant corticosterone dose (2.0 mg/kg, ip; 40 min pretreatment) that resulted in plasma levels (approximately 360 ng/ml) that were comparable to those measured after footshock (n = 6). The inability of the glucocorticoid receptor (GR) antagonist RU-38486 at a dose that resulted in central GR occupation to block this effect of corticosterone (12.5 mg/kg, sc; n = 10) suggests a rapid, non-GR mechanism of action. The actions of corticosterone likely involved effects on dopamine in the nucleus accumbens (NAc) since bilateral intra-NAc corticosterone delivery (0.05 µg/0.3 µl/side delivered over 1 minute) also potentiated cocaine-induced reinstatement (n = 10) while intra-NAc administration of the dopamine receptor antagonist, fluphenazine (30 nmol/side) blocked potentiated reinstatement following systemic corticosterone administration (n = 11). Systemic (ip) corticosterone pretreatment also potentiated the extracellular dopamine response to low-dose cocaine in the NAc as measured by *in vivo* microdialysis (significant increase in cocaine-induced AUC over a 2-hr period vs. vehicle; n = 10-12/group) and this effect was likely attributable in part to reduced clearance of dopamine via a dopamine transporter- (DAT-) independent mechanism, since corticosterone administration decreased dopamine clearance in the NAc as measured by fast scan cyclic voltammetry in rats treated with a saturating dose of the selective DAT blocker, GBR 12909 (15 mg/kg, ip; n = 5/group). We hypothesized that this mechanism involves corticosterone inhibition of organic cation transporter 3 (OCT_3) mediated dopamine clearance. OCT_3 is a high capacity, glucocorticoid-sensitive monoamine transporter expressed adjacent to tyrosine hydroxylase terminals in the NAc. In support of this hypothesis, pretreatment with normetanephrine (2.5 mg/kg, ip), a non-glucocorticoid OCT_3 inhibitor, mimicked corticosterone's potentiating effect on low-dose cocaine-induced reinstatement (n = 10).
Conclusions: Altogether, these findings pose reduced OCT_3 clearance of dopamine within the NAc as a potential mechanism through which stress and corticosterone can "set the stage" for use in recovering cocaine addicts, thereby heightening susceptibility to relapse.
Keywords: relapse, glucocorticoid, stress, cocaine, dopamine, OCT_3, reinstatement
Disclosure: P. Gasser, Nothing to Disclose; E. Graf, Nothing to Disclose; D. Baker, **Part 1:** Co-founder, director, and shareholder, Prementis Pharmaceuticals, **Part 2:** Prementis Pharmaceuticals, **Part 4:** Sponsored research agreement with Prementis Pharmaceuticals; J. McReynolds, Nothing to Disclose; J. Hill, Nothing to Disclose; A. Ebben, Nothing to Disclose; C. Chan, Nothing to Disclose; M. Robble, Nothing to Disclose; O. Vranjkovic, Nothing to Disclose; D. Wheeler, Nothing to Disclose; R. Wheeler, Nothing to Disclose; J. Mantsch, **Part 1:** Co-founder, shareholder, and paid consultant with Prementis Pharmaceuticals, **Part 2:** Prementis Pharmaceuticals.

T62. Basolateral Amygdala Microinfusion of Neuropeptide S (NPS) Rescues Behavior in a Rat Model of Posttraumatic Stress Disorder (PTSD) by Increasing Expression of Brain Derived Neurotrophic Factor and Neuropeptide YY1 Receptor

Hagit Cohen*, Nitsan Kozlovsky, Zeev Kaplan , Joseph Zohar, Aleksander Mathé

Ministry of Health, Beer-Sheva Mental Health Center, Beer-Sheva, Israel

Background: Neuropeptide S (NPS), mainly localized in clusters of cells around Locus coeruleus and with a wide receptor (NPSR1) distribution in the limbic areas, is an anxiolytic and arousal peptide in rodents while in humans it is associated with panic disorders (Xu et al 2004; Reinscheid et al 2005; Domschke et al 2011). We have shown that NPS given centrally has potent anxiolytic effects in rat and mouse models of high anxiety-like behavior as well as in the Flinders Sensitive Line rat, a genetic model of depression, where it affects anxiety-like but not depression-like behavior (Slattery et al, in review; Wegener et al 2011). In the previous study (Cohen et al 2012) we demonstrated a strong association between the magnitude of behavioral responses to predator scent stress (PSS) and patterns of decreased neuropeptide Y (NPY) expression in brain. Animals whose behavior was extremely disrupted (EBR) selectively displayed significant down-regulation of NPY in the hippocampus, periaqueductal gray, and amygdala compared with animals whose behavior was minimally (MBR) or partially (PBR) disrupted, and with unexposed controls. NPY infused bilaterally into dorsal hippocampus significantly reduced prevalence rates of EBR and reduced trauma-cue freezing responses. In an ongoing series of experiments to further elucidate neurobiological correlates of behavior in PTSD and dissect anxiolytic versus antidepressant actions of NPY (conceivably involving amygdala, respectively hippocampus and frontal cortex) instead

of injecting NPY into the dorsal hippocampus, we injected the anxiolytic peptide NPS into basolateral amygdala (BLA).
Methods: Anesthetized rats were restrained in a stereotactic apparatus and a 26-gauge stainless steel guide cannula implanted bilaterally into amygdala. A needle was placed in the guide cannula to prevent clogging. Following one week recovery the rats were exposed to PSS or fresh unused litter for 15 min and NPS or vehicle infused 60 min later. After additional 7 days the behaviors were assessed by the elevated plus-maze (EPM) and acoustic startle response (ASR) tests, performed consecutively. After 24 h the brains were perfused with paraformaldehyde. Frozen coronal sections were obtained and stained for immunohistochemistry. A computer-assisted image analysis system was used for quantitative analysis of the number of immunoreactive (IR) NPY, NPYY1R, and brain derived neurotrophic factor (BDNF) positive cells in the hippocampus that was divided into three separately counted areas: CA1, CA3 and dentate gyrus (DG). Corticosterone in serum was measured by ELISA.
Results: PSS exposure increased all indices of anxiety behavior, e.g. open arms entries and time spent in open arms ($p's < 0.02$). Immediate post-exposure treatment with NPS had marked protective effect; no animal treated with NPS displayed EBR. Interestingly, NPS decreased ASR in both exposed and unexposed animals. Consistently with previous experiments, exposure significantly reduced NPY ($p's < 0.02$) as well as NPYY1R and BDNF expression ($p's < 0.001$) in CA1, CA3 and DG. NPS microinfusion into BLA increased NPYY1R and BDNF ($p < 0.001$) but had no effect on NPY in CA1, CA3 and DG. Serum corticosterone was increased following scent stress ($p < 0.05$). Moreover, in line with its arousal properties, NPS further elevated corticosterone levels 40 min after the injection.
Conclusions: Present experiments demonstrate the high reproducibility of PSS as an animal model of PTSD. In similarity to the previous experiment (Cohen et al 2012) PSS reduced expression of BDNF, NPY and NPYY1 receptor in hippocampus. The most salient new finding was that the anxiolytic peptide NPS completely abolished the extreme behavioral response to PSS. Moreover, it restored the decreased expression of BDNF and, unexpectedly, NPYY1 receptor. Since NPS did not affect the decreased expression of NPY, it is conceivable that NPS acts, directly or indirectly, on NPYY1 receptor. In order to dissect underpinning biology of anxiety versus depression we are exploring effects of NPS and NPY injected into hippocampus and/or amygdala on behavior and biochemistry of frontal cortex, PAG, hippocampus and amygdala.
Keywords: Posttraumatic stress disorder, Animal model, Anxiety, Neuropeptide S, Neuropeptide Y
Disclosure: H. Cohen, Nothing to Disclose; N. Kozlovsky, Nothing to Disclose; Z. Kaplan, Nothing to Disclose; J. Zohar, Nothing to Disclose; A. Mathé, Nothing to Disclose.

T63. Inhibition of the Fatty Acid Amide Hydrolase (FAAH) in Acute Schizophrenia – A Mechanistically New Approach to its Treatment

F. Markus Leweke*, Martin Hellmich, Franziska Pahlisch, Laura Kranaster, Dagmar Koethe

Central Institute of Mental Health, Mannheim, Germany

Background: New pharmacological targets for the treatment of schizophrenia are urgently required. We initially identified one of the two major endocannabinoids, anandamide, as a counterbalancing if not protective factor in paranoid schizophrenia. Most recently, we reported that increasing levels of anandamide by blocking its metabolization by cannabidiol, a purified phytocannabinoid, significantly ameliorates psychotic symptoms in acute schizophrenia (Leweke et al., Transl Psychiatry 2012). Here, we report on the results of the first clinical trial comparing cannabidiol vs. placebo in acutely exacerbated, first-break paranoid schizophrenia patients.
Methods: We performed a randomized, double-blind, placebo-controlled, cross-over clinical trial in acute, antipsychotic-naive, first-break paranoid schizophrenia patients, fulfilling diagnostic criteria of DSM-IV. 29 patients were treated after written informed consent with either cannabidiol (600 mg per day) or placebo for 14 days and than switched to the corresponding cross-over condition. Additional patients to gain a total of 18 patients treated per protocol replaced dropouts. Serum was taken at baseline and on days 14 and 28. In addition, 14 patients provided cerebrospinal fluid (CSF) at baseline and day 28 for biomarker investigations.
Results: Cannabidiol significantly improved psychotic symptoms in the cannabidiol-placebo condition during the first 14 days of treatment when compared to baseline. A MMRM analysis of all randomized patients ($n = 29$) yielded a mean improvement of 2.4 points (standard error 3.0) on PANSS total in favor of cannabidiol (vs. placebo), albeit not statistically significant. Only one patient on sequence cannabidiol-placebo terminated treatment early (last seen at visit 3) whereas 10 patients terminated early on sequence placebo-cannabidiol. The most frequent reason given was worsening of symptoms (5/11 patients). In addition, cannabidiol was detectable in serum of almost all patients in the cannabidiol-placebo group. Side-effects of cannabidiol were on the level of placebo.
Conclusions: Although limited by design issues (cross-over), duration of treatment (14 days), carry-over effects (serum levels of cannabidiol), and relevant placebo-response rates, this is the second study to provide evidence for antipsychotic properties of cannabidiol accompanied by a superior side-effect profile. Future placebo-controlled parallel-group trials studying the antipsychotic properties of cannabidiol in acute schizophrenia are necessary to provide further evidence for its efficacy in the treatment of this devastating disease.
Keywords: schizophrenia, endocannabinoid system, anandamide, clinical trial, cannabidiol
Disclosure: F. Leweke, **Part 1:** Shareholder: curantis UG (ltd.); Speaker/Advisory Board: AstaZeneca Germany, Brystol-Myers-Squibb Germany, Lilly Germany, Lundbeck Germany; Editorial board: future science group, **Part 2:** Central Institute of Mental Health; M. Hellmich, Nothing to Disclose; F. Pahlisch, Nothing to Disclose; L. Kranaster, Nothing to Disclose; D. Koethe, Nothing to Disclose.

T64. A Pilot Study on the Effects of Single Dose Intranasal Oxytocin on Social Cognition in Schizophrenia

Michael C. Davis, Junghee Lee, William Horan, Michael F. Green, Stephen R. Marder*

Semel Institute at University of California, Los Angeles, California

Background: Deficits in social cognition (e.g., emotion processing, social perception, and mental state attribution) are common in individuals with schizophrenia and predict poor community functioning. Given the current limitations of psychosocial treatments and the lack of pharmacological treatments for social cognitive deficits, the development of novel therapeutic agents could greatly enhance the treatment of schizophrenia. The oxytocin system, given its importance in affiliative behaviors and the social brain, has garnered much recent attention in research on schizophrenia and other disorders associated with social cognitive deficits. In this pilot study, we test the hypothesis that a single dose of intranasal oxytocin will improve social cognitive functioning in individuals with schizophrenia.
Methods: Twenty-four male veterans between the ages of 26 and 56 who met the DSM-IV-TR criteria for schizophrenia were enrolled in this study. Baseline assessments of "low level" (1. facial affect perception, 2. social perception) and "high level" (3. detection of sarcasm and deception, 4. empathy) social cognition were performed, as were assessments of symptom severity (Positive and Negative Syndrome Scale and Clinical Global Impression). One week later, patients received a single dose of 40 IU intranasal oxytocin or placebo, assigned by double-blind randomization, and the social cognition assessment battery and symptom assessments were repeated. The pre-specified primary endpoint was the change

on a composite score based on the four social cognitive tests between baseline and treatment visits.
Results: Twenty-three individuals completed the entire study. The treatment and assessment battery were well-tolerated, and subjects were unable to guess which treatment they had received. There were no significant differences between the groups on the social cognition composite score (+ 0.10 versus + 0.23 for the mean change in z-score in the placebo and oxytocin groups, respectively) or on any of the component social cognitive measures. Post-hoc responder analysis showed 36% of subjects receiving oxytocin had $\geqslant$0.5 standard deviations improvement from baseline on the social cognition composite score versus 8% of subjects receiving placebo. There were no differential changes across the groups in psychiatric symptoms.
Conclusions: This study demonstrates the feasibility and tolerability of intranasal oxytocin and assessments of multiple domains of social cognition in patients with schizophrenia. Results from this initial pilot study found that a single dose of intranasal oxytocin did not improve social cognition in schizophrenia. Repeated doses of intranasal oxytocin may be necessary to exert a significant effect on social cognition in schizophrenia.
Keywords: schizophrenia, oxytocin, social cognition
Disclosure: M. Davis, Nothing to Disclose; J. Lee, Nothing to Disclose; W. Horan, Nothing to Disclose; M. Green, **Part 1:** Consultant – Abbott Laboratories, Amgen, Cypress, Lundbeck, and Teva, Speaker - Otsuka and Sunovion; S. Marder, **Part 1:** Consultation and Advisory Boards: Amgen, Astellas, Abbott, Roche, Targacept, Otsuka, Pfizer, Shire, Lundbeck, Genentech, Research Support: Glaxo Smith Kline, Novartis, Sunovion, Psychogenics, Stockholder: Med Avante.

T65. Alterations in Synaptic Potentiation and Glutamatergic Signaling in Nicotine Abuse

Cassandra Gipson*, Yonatan Kupchik, Kathryn Reissner, Peter Kalivas

Medical University of South Carolina, Charleston, South Carolina

Background: Addiction to nicotine produces long-lasting, stable changes in brain synaptic physiology that might contribute to the vulnerability to relapse. However, it is not known if synaptic changes are initiated by and contribute to nicotine relapse. Cues associated with nicotine use can precipitate relapse. Using a rat model of cue- and nicotine-induced reinstatement of nicotine-seeking, we quantified synaptic plasticity in the nucleus accumbens core (NAcore) via morphological changes in dendritic spine head diameter and electrophysiological estimates of excitatory synaptic transmission (AMPA:NMDA ratio).
Methods: Male Sprague-Dawley rats were trained to press an active lever for delivery of chow pellets prior to self-administration of nicotine (0.02 mg/kg/infusion) on an FR1 schedule during 2 h sessions each day, for approximately two weeks. A lever press resulted in a nicotine infusion paired with presentation of light and tone cues. Following nicotine self-administration, rats were placed in an extinction training phase in which a lever press no longer resulted in drug or drug-paired cues. Rats were either given a nicotine injection (150 μg/kg, s.c.) or contingent cues in which lever press responding led to contingent presentations of the compound cue stimulus previously paired with nicotine infusions, but no nicotine was delivered. Responding to the lever previously associated with drug delivery was the measure of nicotine-seeking behavior. After the appropriate timepoint during reinstatement (0, 15 or 45 min), rats were sacrificed for western blots, spine morphology, or electrophysiological measures. NAcore tissue for western blots was dissected, and membrane fractionation was prepared. For spine morphology, lipophilic dye was diolistically delivered onto NA slices, and dendritic spines were then imaged and analyzed. NA slices were also taken from animals for electrophysiology, and AMPA and NMDA currents were recorded in whole cell patch-clamp configuration.
Results: Withdrawal from nicotine self-administration caused a basal increase in spine head diameter and ratio compared to yoked saline animals, and cue-induced reinstated nicotine seeking elicited further increases in head diameter and AMPA:NMDA ratio within 15 min of the priming stimulus. Nicotine-induced reinstatement elicited a further increase in spine head diameter after 45 min of the priming stimulus. Enlargement of dendritic spines has been associated with increased synaptic strength, as well as an upregulation in surface expression of GluR subunits of AMPA and NR2B-containing NMDA receptors. Importantly, we found that both GluR1 and NR2B were upregulated after extinction from nicotine self-administration in parallel with an increase in spine head diameter and AMPA:NMDA ratio.
Conclusions: These results show that rapid synaptic potentiation in the NAcore may underpin relapse to nicotine use, and inhibition of GluR1 and NR2B may be important pharmacotherapeutic avenues in reducing nicotine relapse.
Keywords: Nicotine, Addiction, Synaptic plasticity, Relapse, Glutamate
Disclosure: C. Gipson, Nothing to Disclose; Y. Kupchik, Nothing to Disclose; K. Reissner, Nothing to Disclose; P. Kalivas, Nothing to Disclose.

T66. Serum IgG Antibodies Against the NR1 Subunit of the NMDA Receptor Not Detected in Schizophrenia

Joseph C. Masdeu*, Ana González-Pinto, Carlos Matute, Sonia Ruiz de Azúa, Aitor Palomino, Jose de Leon, Karen F. Berman, Josep Dalmau

National Institutes of Health Intramural Research Program, Bethesda, Maryland; New York Medical College

Background: A consensus exists that schizophrenia is not a single disease, but the final pathway of a variety of still unknown neurobiological derangements. A neurodevelopmental disorder is probably most frequent, but some patients may have an autoimmune etiology, as suggested by several lines of evidence. First, although histological inflammatory changes have not been detected in the brain of patients with schizophrenia, inflammation-related genes are up-regulated in brain tissue (Saetre et al., 2007; Fillman et al., 2012). Second, several of the leading risk genes associated with schizophrenia in genome-wide association studies code for proteins critical for immunity (Stefansson et al., 2009). This is not the case for other common brain disorders, such as Alzheimer or Parkinson disease, but it is the case for multiple sclerosis, an autoimmune disease. Third, a group of synaptic autoimmune brain diseases has been recently identified with characteristics compatible with the known neurobiology of schizophrenia. Particularly interesting are auto-antibodies directed against the N-acetyl methyl D-aspartate receptor (NMDAR) (Dalmau et al., 2008). These antibodies effect diminished NMDAR activity, now generally accepted to be one of the hallmarks of schizophrenia. NMDAR dysfunction impairs brain networks supporting cognition and emotion. As a result, patients develop psychotic symptoms (Dalmau et al., 2008). Structural neuroimaging is often normal. On brain biopsy, there are normal or non-specific findings. The responsible anti-synaptic antibodies have been detected in cerebrospinal fluid (CSF) and, in a subset of patients, in serum as well. The main difference with the schizophrenic syndrome is that these patients are much sicker, most developing a catatonic state and requiring intensive care (Dalmau et al., 2008). But, as well illustrated by multiple sclerosis, brain autoimmune disorders range between severe forms and milder ones, when the autoimmune attack is tempered by natural regulators of the immune response. It is reasonable to postulate that a milder form of anti-NMDAR antibody disease may occasionally be the cause of the schizophrenic syndrome and if so, antibodies may be found in the CSF or serum. We tested this hypothesis using sera from patients with their first psychotic episode.
Methods: We studied patients with their first psychotic episode referred to the regional psychiatric center of the province of Alava, Spain, and healthy controls. All were enrolled after written informed consent according to protocols approved by the local IRB. Blood was drawn and sera were frozen for subsequent study.

After a one-year follow up, sera of patients who then met DSM-IV-TR criteria for schizophrenia-spectrum disorders and controls were tested for antibodies to NR1 and other cell surface antigens using three criteria (immunohistochemistry on rat brain slices and dissociated rodent hippocampal neurons, and a cell-based assay in which HEK cells recombinantly express NMDAR), as previously reported (Dalmau et al., 2008).
Results: Patients (n = 80) and healthy controls (n = 40) groups did not differ statistically in age (29.4 ± 9.9 and 30.7 ± 9.4 years), or sex (28 and 38 percent women). Anti-NR1 IgG antibodies were not detected in either group. Both had four cases with sera reactive to other, still unidentified, neuronal surface antigens.
Conclusions: Our findings and a study of seven patients with schizophrenia (Rhoads J et al., 2011) fail to support the hypothesis that NMDAR IgG antibodies are present in the sera of patients with schizophrenia. Although another study (Zandi MS et al., 2011) did report NMDAR antibodies in the sera of some schizophrenia patients, test specificity was lower (only one of the above criteria was applied) and there was no control group; differences in the clinical diagnosis could also play a role in the discrepant findings. It should be noted that our study does not rule out that some patients could have antibodies only in CSF but not in serum. Additionally, antibodies could be present in patients with acute psychosis not meeting DSM-IV diagnostic criteria at one-year.
Keywords: Schizophrenia NMDA receptor Antibodies Autoimmune
Disclosure: J. Masdeu, Nothing to Disclose; A. González-Pinto, Nothing to Disclose; C. Matute, Nothing to Disclose; S. Ruiz de Azúa, Nothing to Disclose; A. Palomino, Nothing to Disclose; J. de Leon, Nothing to Disclose; K. Berman, Nothing to Disclose; J. Dalmau, **Part 4:** Dr. Dalmau has a patent on a procedure to determine anti-NMDA antibodies and receives royalties from Euroimmun, a company that provides this procedure commercially.

T67. Abnormalities of Glutamate Microdomains in Schizophrenia

Robert McCullumsmith*, Dan Shan, Joy Roche, Vahram Haroutunian, James Meador-Woodruff, Rosalinda C. Roberts

The University of Alabama at Birmingham, Birmingham, Alabama

Background: Glutamate microdomains are specialized structures localized to astrocytic processes and comprised of protein complexes that facilitate glutamate release, Na^+/K^+ exchange, ATP synthesis, and regulation of Ca^{2+} stores. We postulate that glutamate microdomains help regulate extrasynaptic glutamate levels, modulating the activation of several types of glutamate receptors expressed on astrocytes and neurons in or near these domains. We also propose that diffusion of glutamate between the synaptic cleft and these microdomains is carefully limited by the dense expression of glutamate transporters, which bind and transport glutamate. Thus, the spatial distribution of glutamate synapses, extrasynaptic glutamate microdomains, and clusters of glutamate transporters is critically important for maintenance and function of glutamate-mediated connectivity; alterations in the spatial integrity of these components could lead to a loss of input specificity and altered synchronization of neuronal circuits. Although the treatment of schizophrenia with antipsychotic medications revolutionized the clinical management of this illness, most patients with schizophrenia have persistent symptoms despite multiple trials of antipsychotic medicines. Recently, new strategies for the treatment of schizophrenia have emerged, including modulation of extrasynaptic glutamate receptors, highlighting the importance of understanding the extrasynaptic milieu. We hypothesize that the localization, structure and composition of glutamate microdomains is altered in the deep layers of the frontal cortex in subjects with schizophrenia.
Methods: Using electron microscopy, immunoisolation, immunofluorescence, mass spectroscopy, and subcellular fractionation, we investigated the localization, structure and composition of glutamate microdomains in the human frontal cortex. Using the same techniques, we also evaluated the integrity of glutamate microdomains in subjects with schizophrenia and a comparison group.
Results: Using immunoisolation and mass spectroscopy, we identified a protein complex that is an element of a putative glutamate microdomain in the human frontal cortex. This complex includes glutamate transporters, mitochondria-associated enzymes, Na + /K + ATPases, as well as several signaling and structural molecules. Using electron microscopy, we assessed the ultrastructural localization of the glutamate transporter EAAT2 (a central component of this microdomain) and its proximity to asymmetric (excitatory) synapses. We also used immunofluorescence to demonstrate colocalization of several microdomain components in the human cortex. In subjects with schizophrenia, we found changes in the cellular localization of EAAT2, as well as changes in EAAT2 splice variant expression in an enriched fraction containing extrasynaptic membranes. We also found a change in the subcellular localization of the glycolytic enzyme hexokinase in schizophrenia, with a decrease in coupling to mitochondria.
Conclusions: We investigated the composition and localization of microdomains in the human frontal cortex. These data provide a novel view of the extrasynaptic domains that have repeatedly been shown to have profound physiologic roles in the regulation of neuronal activity and the synchrony of neuronal networks. We also found changes in the subcellular localization of microdomain components in schizophrenia, suggesting that the integrity of these domains is altered in this illness.
Keywords: schizophrenia, glutamate, mass spectroscopy, microdomain, frontal cortex
Disclosure: R. McCullumsmith, Nothing to Disclose; D. Shan, Nothing to Disclose; J. Roche, Nothing to Disclose; V. Haroutunian, Nothing to Disclose; J. Meador-Woodruff, Nothing to Disclose; R. Roberts, Nothing to Disclose.

T68. Upregulation in the Expression of Key Serotonergic, Noradrenergic, and Cholinergic Genes in the Lower Brainstem in Major Depression: Neurobiological Substrate for Somatic Symptoms?

Aneesh Tyle, Nina S. Amilineni, Danielle A. Simpson, Edward G. Jones, William E. Bunney, Huda Akil, Stanley J. Watson, Ilan A. Kerman*

University of Alabama at Birmingham, Birmingham, Alabama

Background: In addition to affective disturbances, major depressive disorder (MDD) is characterized by physical symptoms, including fatigue, increased pain sensitivity, sleep alterations, and changes in appetite. Presence of such physical symptoms is associated increased severity of the illness and is also associated with significant medical comorbidities. There is a strong bidirectional relationship between MDD and heart disease, as well with diabetes and with chronic pain, yet the underlying pathophysiology remains obscure. Human post-mortem studies in the MDD brain have documented alterations in the organization of pontomesencephalic serotonergic and noradrenergic cell groups that send ascending projections to the forebrain, and the dysregulation of these ascending circuits is thought to contribute to the cognitive and affective symptoms of MDD. We hypothesized that in addition to the ascending circuits, the descending monoaminergic and related circuits, which regulate motor and autonomic functions along with pain sensitivity, are also altered in MDD.
Methods: We collected post-mortem human brainstem samples from subjects with MDD and from psychiatrically-normal comparison individuals. Using a combined neurochemical and histological staining approach we mapped the locations of the serotonergic, noradrenergic, and cholinergic cell groups in the lower brainstem. Using radioactive *in situ* hybridization we then examined potential alterations in the expression of key synthetic enzymes in the production of serotonin, norepinephrine, and acetylcholine, including tryptophan hydroxylase 2 (TPH2), tyrosine hydroxylase (TH), and choline acetyltransferase (ChAT), respectively. In addition, we also examined expression of the serotonin 1B receptor (HTR1B), an inhibitory autoreceptor implicated in the etiology of depression.

Results: We detected significant upregulation in the expression of all of these genes within lower brainstem nuclei in the MDD brain. TPH2 expression was increased within the ventromedial medulla (nucleus raphe magnus (RMg) and the gigantocellular nucleus pars alpha (GiA)), and within raphe pontis. Expression of HTR1B was likewise increased within the ventromedial medulla (including RMg, GiA, raphe pallidus, and ventral gigantocellular nucleus) as well as within the ventrolateral medulla. TH expression was increased within the A1/C1 and A2/C2, but not within the A5 and ventral subcoeruleus, cell groups. We also detected increased ChAT gene expression within the 6th nerve nucleus.
Conclusions: These data indicate upregulation in MDD in the expression of several genes that play key roles in the regulation of serotonergic, noradrenergic, and cholinergic neurotransmission in the lower brainstem and within spinally-projecting circuits. These changes likely reflect alterations in the signaling of these neurotransmitter systems and may contribute to the emergence of physical symptoms of MDD as well as its medical comorbidities.
Keywords: mood disorder, *in situ* hybridization, medical comorbidity, medulla
Disclosure: A. Tyle, Nothing to Disclose; N. Amilineni, Nothing to Disclose; D. Simpson, Nothing to Disclose; E. Jones, Nothing to Disclose; W. Bunney, **Part 1:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the Hudson Alpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; H. Akil, **Part 1:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the Hudson Alpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; S. Watson, **Part 1:** The authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium, which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the Hudson Alpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications; I. Kerman, Nothing to Disclose.

T69. Alterations of Endogenous Cannabinoids in Complex PTSD and Borderline Personality Disorder

Juliane K. Mueller*, Carola Schaefer, Frank Enning, J. Malte Bumb, Martin Hellmich, Dagmar Koethe, Christian Schmahl, Martin Bohus, F. Markus Leweke

Central Institute of Mental Health, Mannheim, Germany

Background: The endocannabinoid system plays an important role in the pathophysiology of psychiatric disorders like schizophrenia. Due to its neuromodulatory potential, its role in emotion regulation and in extinction of aversive memory, the endocannabinoid system might be another potential candidate system, affecting a broad range of psychopathology in both, posttraumatic stress disorder (PTSD) and/or borderline personality disorder (BPD).
Methods: We addressed the question by analyzing serum levels of the endogenous cannabinoids anandamide and 2-arachidonoyl-*sn*-glycerol (2-AG) and the structurally related endogenous lipids oleoylethanolamide and palmitoyletnanolamide. Based on our previous approach we developed and validated a specific and sensitive method using high performance liquid chromatography coupled with tandem mass spectroscopy (HPLC-MS/MS). We analyzed human serum samples from patients suffering from BPD ($n = 23$) or PTSD ($n = 21$) as well as from matched healthy controls ($n = 34$).
Results: Levels of anandamide were significantly elevated in both PTSD and BPD patients (Figure 1A), while palmitoylethanolamide was significantly elevated in BPD with a trend in PTSD and oleoylethanolamide was significantly elevated in PTSD with a trend in BPD when compared to controls. In contrast, 2-AG was significantly elevated in BPD when compared to both, controls and PTSD, where no alteration in 2-AG was found. An independent analysis within BPD revealed no difference between those patients suffering PTSD in parallel and those who did not.
Conclusions: Our data rise evidence that the endocannabinoid system may play a functional role in the pathophysiology of both PTSD and BPD and warrant further investigation of this contribution.
Keywords: PTSD, Borderline personality disorder, endocannabinoid system, anandamide, 2-AG
Disclosure: J. Mueller, Nothing to Disclose; C. Schaefer, Nothing to Disclose; F. Enning, Nothing to Disclose; J. Bumb, Nothing to Disclose; M. Hellmich, Nothing to Disclose; D. Koethe, Nothing to Disclose; C. Schmahl, Nothing to Disclose; M. Bohus, Nothing to Disclose; F. Leweke, **Part 1:** Shareholder: curantis UG (ltd.); Speaker/Advisory Board: AstaZeneca Germany, Brystol-Myers-Squibb Germany, Lilly Germany, Lundbeck Germany; Editorial board: future science group, **Part 2:** Central Institute of Mental Health.

T70. Glutamate Signaling is Reduced and GABA Signaling Unaffected in Hippocampus in Schizophrenia

Ana D. Stan*, Subroto Ghose, Yan Fang, Perry Mihalakos, Stephanie Morris, Sandeep Ganji, Changho Choi, Carol A. Tamminga

UT Southwestern, Dallas, Texas

Background: The role of hippocampal dysfunction in schizophrenic psychosis is widely acknowledged. Yet, the question of whether this dysfunction is mediated through excitatory or through inhibitory neurotransmission, or both, is often debated. To answer this question stringently requires informative measures of both glutamate and GABA signaling in human hippocampus. In the present study we implement the use of two convergent methodologies, one with dynamic advantages (proton magnetic resonance spectroscopy – 1H MRS) and another with high-resolution information (postmortem tissue biochemistry). Specifically, we used proton to measure *in vivo* hippocampal glutamate and gamma-aminobutyric (GABA) concentrations in a cohort of volunteers with schizophrenia in comparison with healthy controls. To refine these *in vivo* measurements further, we quantified postmortem tissue markers of excitatory and inhibitory neurotransmission, ie the NR1 subunit of the *N*-methyl-D-aspartate (NMDA) receptor and glutamic acid decarboxylase (GAD) 67, the main enzyme for GABA synthesis. We sampled hippocampal subfield tissue from schizophrenia (SZ) and normal control (NC) subjects by subfield, in order to generate a regional map of the excitatory and inhibitory transmission in the hippocampus.
Methods: MRS data were collected from left hippocampus in schizophrenia ($N = 20$) and normal ($N = 17$) volunteers at 3T and analyzed with spectral fitting. Protein levels of NR1 subunit of the NMDA receptor and GAD67 were quantified by Western blotting in each subfield in the postmortem hippocampus derived from 14 subjects with schizophrenia and 14 matched controls.
Results: Glutamate levels as measured by MRS were significantly decreased from normal in the hippocampus of volunteers with schizophrenia: (NC:* 0.89 ± 0.11; SZ:* 0.81 ± 0.09; $p = 0.01$); there was no difference in the GABA levels between groups ((NC:* 0.33 ± 0.06; SZ:* 0.35 ± 0.09, $p = 0.49$). In the postmortem tissue, we found NR1 protein levels reduced specifically in dentate gyrus (DG) in the schizophrenia group (NC:* 3.34 +/− 1.23; SZ:*

2.28 ± 0.79, $t^* = 2.5$, $df^* = 22$, $p^* = 0.021$), a reduction of 32% from normal. In the other subfields, NR1 was not significantly changed, albeit was consistently lower than normal: GAD67 concentrations by subfield in schizophrenia hippocampus showed no significant change in any subfield.
Conclusions: The results show a significant decrease in glutamate itself in hippocampus assessed by MRS, an *in vivo* finding which is reflected in the parallel decrease *in vitro* in NR1 protein in dentate gyrus. This protein outcome is consistent with the MRS result and suggests significant sensitivity of the MRS measure. On the other hand, we found no change *in vivo* in GABA by MRS, a finding which we show to be consistent with the lack of change in GAD67 protein *in vitro* in the hippocampal subfield tissue from schizophrenia. The *in vivo* and *in vitro* findings in these schizophrenia cohorts converge and together suggest that, from a molecular perspective, it is predominantly the excitatory system within hippocampus that is altered in schizophrenia
Keywords: schizophrenia; magnetic resonance spectroscopy; glutamate; GABA; hippocampus
Disclosure: A. Stan, Nothing to Disclose; S. Ghose, Nothing to Disclose; Y. Fang, Nothing to Disclose; P. Mihalakos, Nothing to Disclose; S. Morris, Nothing to Disclose; S. Ganji, Nothing to Disclose; C. Choi, Nothing to Disclose; C. Tamminga, **Part 1:** Astellas – *Ad Hoc* Consultant, Eli Lilly Pharmaceuticles – *Ad Hoc* Consultant, Intra-cellular Therapies (ITI, Inc.) – Advisory Board, drug development, Lundbeck, Inc – *Ad Hoc* Consultant, PureTech Ventures – *Ad Hoc* Consultant, **Part 2:** American Psychiatric Association – Deputy Editor.

T71. Functional Brain Basis of Hypnotizability

David Spiegel*, Fumiko Hoeft, John DE. Gabrieli, Susan Whitfield-Gabrieli, Brian Haas, Roland Bammer, Vinod Menon

Stanford University School of Medicine, Stanford, California

Background: The main goal of the study was to investigate the brain basis of hypnotizability.
Methods: Design: Cross sectional, *in-vivo* neuroimaging study. Setting: Academic medical center at Stanford University School of Medicine. Patients: 12 adults with high and 12 adults with low hypnotizability. Main Outcome Measures: (1) functional MRI (fMRI) to measure functional connectivity networks at rest including default-mode, salience and executive-control networks, (2) structural T1 MRI to measure regional grey and white matter volumes, and (3) diffusion tensor imaging (DTI) to measure white matter microstructural integrity.
Results: High- compared to low-hypnotizable individuals showed greater functional connectivity between left dorsolateral prefrontal cortex (DLPFC), an executive-control region of the brain, and the salience network composed of the dorsal anterior cingulate cortex (dACC), anterior insula, amygdala, and ventral striatum, involved in detecting, integrating, and filtering relevant somatic, autonomic, and emotional information, using independent component analysis (ICA). Seed based analysis confirmed elevated functional coupling between the dACC and the DLPFC in high, compared to low, hypnotizables. These functional differences were not due to variation in brain structure in these regions, including regional grey and white matter volumes and white matter microstructure.
Conclusions: Our results provide novel evidence that altered functional connectivity in DLPFC and dACC may underlie hypnotizability. Future studies focusing on how these functional networks change and interact during hypnosis are warranted.
Keywords: hypnosis, fMRI, resting-state functional connectivity, DLPFC, ACC
Disclosure: D. Spiegel, Nothing to Disclose; F. Hoeft, Nothing to Disclose; J. Gabrieli, Nothing to Disclose; S. Whitfield-Gabrieli, Nothing to Disclose; B. Haas, Nothing to Disclose; R. Bammer, Nothing to Disclose; V. Menon, Nothing to Disclose.

T72. Changes in Fusiform Gyrus Associated with Face Processing in Social Anxiety Disorder, Before and After Treatment

Ardesheer Talati*, Spiro Pantazatos, Joy Hirsch, Franklin R. Schneier

Columbia University and New York State Psychiatric Institute, New York, New York

Background: The fusiform gyrus (FG), corresponding to Brodmann's Area 37 of the occipitotemporal cortex, is particularly salient for social anxiety disorder (SAD) given its role in processing of social constructs and facial expressions. We previously reported in two independent samples that compared to healthy controls, subjects with SAD had increased grey matter (GM) within this region. We here further test whether (1) these morphological differences are accompanied by functional differences related to processing of facial emotions, a cardinal feature of social anxiety; and (2) whether any functional differences identified in FG are altered following eight weeks of SSRI (paroxetine) treatment.
Methods: The study included 17 cases with generalized SAD, and 17 healthy controls. Diagnoses were confirmed with a SCID-IV interview. Images were collected on a 1.5T GE Signa MRI scanner at baseline and after eight weeks of paroxetine treatment. While in the scanner, subjects viewed a battery of standardized faces bearing neutral or angry expressions, and were asked to identify either the facial expression (explicit) or gender (implicit). Data were analyzed in SPM8. Results reported are based on a cluster size of $k = 147$, $p \leqslant .005$. All group differences were adjusted for age and gender.
Results: As compared to healthy controls, the SAD group showed decreased activation of the FG in both hemispheres during viewing of faces with angry (relative to neutral) expressions. Following SSRI treatment, SAD symptoms were significantly improved. Within the SAD group, there was a significant post-treatment increase in predominantly right FG activity in response to viewing angry faces. Similar post-treatment changes were observed when the faces were viewed implicitly, suggesting that the neurobiological processes involved are not dependent on conscious registration of the emotional content of stimuli.
Conclusions: The functional differences parallel neuronatomical differences previously identified in both this and other studies. The observations that subjects with SAD initially showed lower FG activation in response to negative faces than controls, but that activation increased following SSRI treatment, provides further support that the FG region may play a core role in the symptomatology of the disorder. Post-treatment increases may reflect processes of decreased avoidance or increased facial encoding that accompany clinical improvement. The relationships between treatment induced changes in SAD symptoms and changes in FG brain activation will also be examined.
Keywords: social anxiety disorder functional MRI fusiform gyrus paroxetine
Disclosure: A. Talati, Nothing to Disclose; S. Pantazatos, Nothing to Disclose; J. Hirsch, Nothing to Disclose; F. Schneier, **Part 1:** Receieved honoraria from Glaxo for two talks at conferences in 2011, **Part 2:** NIMH, New York State, Columbia University.

T73. Markedly Reduced mGluR5 Receptor Binding in Smokers and Ex-smokers Determined by [11C]ABP688 Positron Emission Tomography

Gregor Hasler*, Funda Akkus, Simon M. Ametamey, Valerie Treyer, Cyrill Burger, Anass Johayem, Daniel Umbricht, Baltazar Gomez Mancilla, Judit Sovago, Alfred Buck

Psychiatric University Hospital, Bern, Switzerland

Background: Nicotine addiction is a major public health problem, resulting in primary glutamatergic dysfunction. We measured the glutamate receptor binding in the human brain and provided direct evidence for the abnormal glutamate system in smokers.

Since antagonism of the metabotropic glutamate receptor 5 (mGluR5) reduced nicotine self-administration in rats and mice, mGluR5 is suggested to be involved in nicotine addiction.
Methods: We used positron emission tomography (PET) with the radiolabeled mGluR5 antagonist 3-(6-methyl-pyridin-2-ylethynyl)-cyclohex-2-enone-O-11C-methyl-oxime ([^{11}C]ABP688) (15), which binds with high selectivity to an allosteric site, to measure mGluR5 availability in 14 healthy subjects (non-smokers), 14 smokers, and 10 ex-smokers. The mean duration of nicotine abstinence in ex-smokers was 18.2 weeks (standard deviation, 14.2).
Results: We found a marked global reduction (20.6%; $p < 0.0001$) in the mGluR5 distribution volume ratio (DVR) in the gray matter in smokers. The most prominent reductions were found in the bilateral medial orbitofrontal cortex. Compared to non-smokers, ex-smokers had global reductions in the average gray matter mGluR5 DVR (12.4%; $p < 0.005$). In contrast, the differences in mGluR5 DVR in any brain region between smokers and ex-smokers did not reach statistical significance after Bonferroni correction. In smokers, age was positively correlated with mGluR5 DVR in most regions of interest, and the strongest correlations were found in the putamen. Clinical variables reflecting current nicotine consumption, dependence, and abstinence were not correlated with mGluR5 DVR.
Conclusions: These findings suggest that the reduced mGluR5 may not reflect a simple consequence of nicotine consumption but may represent a precondition of nicotine dependence and/or a trait-like pathogenetic or compensatory change associated with nicotine addiction. This study encourages the development and testing of drugs against addiction that directly target the glutamatergic system.
Keywords: nicotine, addiction, glutamate, mGluR5, positron emission tomography
Disclosure: G. Hasler, Nothing to Disclose; F. Akkus, Nothing to Disclose; S. Ametamey, Nothing to Disclose; V. Treyer, Nothing to Disclose; C. Burger, **Part 1:** Shareholder of PMOD Technologies; A. Johayem, Nothing to Disclose; D. Umbricht, **Part 2:** Empore of F. Hofmann - La Roche ; B. Gomez Mancilla; J. Sovago, **Part 1:** I am an employee of Novartis Pharma AG, **Part 3:** I am an employee of Novartis Pharma AG; A. Buck, Nothing to Disclose.

T74. Imaging the Sensitivity of [123I]5-IA-85380 to Increases in Acetylcholine at the Beta2-Nicotinic Acetylcholine Receptors in Human Subjects

Irina Esterlis*, Jonas Hannestad, Frederic Bois, Andrew Sewell, Rachel Tyndale, John Seibyl, Marina Picciotto, John H. Krystal, Marc Laruelle, Richard Carson, Kelly Cosgrove

Yale University, West Haven, Connecticut

Background: Introduction: Acetylcholine is one of the major neurotransmitters in the brain and has been implicated in psychiatric and medical illnesses. Our evaluation of the nicotinic acetylcholine system (β_2^*-nAChR) *in vivo* in individuals with current and remitted major depressive disorder demonstrated significantly lower receptor availability associated with current depression (and less so with remitted depression) compared to controls. We followed up with a postmortem study to quantify β_2-nAChR density under the conditions where endogenous acetylcholine is washed out, and observed no difference in β_2-nAChR density between individuals with and without major depressive disorder. An interpretation of these results is β_2^*-nAChRs might be lower in depression, and/or that increased acetylcholine concentration in the vicinity of β_2^*-nAChR might reduce the availability of these receptors to the binding of the radioligand. Previously, Fujita and colleagues showed that the high affinity β_2^*-nAChRradioligand [^{123}I]5-IA-85380 ([^{123}I]5-IA) may be sensitive to extracellular increases in acetylcholine in baboons 1; however, such an examination in humans has lagged. Given that acetylcholine is one of the major neurotransmitters in the brain and has been implicated in the psychiatric andmedical illnesses, we developed a paradigm to interrogate the cholinergic system *in vivo* via use of [^{123}I]5-IA single photon emission computed tomography (SPECT) imaging and physostigmine, a centrally-acting acetylcholinesterase inhibitor.
Methods: Six healthy subjects (3 men, 3 women; 31 ± 4.1 yrs) participated in one [^{123}I]5-IA SPECT study and one magnetic resonance imaging (MRI) scan. MRI was used to guide placement of regions of interest for SPECT scans. [^{123}I]5-IA was administered as a bolus plus constant infusion (B/I 7.0 h); total injected dose was 390.2 ± 13.2MBq. After three 30-min baseline scans at 6-8 h post infusion, physostigmine (1-1.5 mg) was administeredIV over 60 min, and nine additional 30-min scans were collected during the next 6 h. The outcome measure was V_s/f_p (specific volume of distribution), calculated as V_T/f_p (estimated receptor availability) minus V_{ND}/f_p (nondisplaceable binding; previously estimated in a smoking to satiety paradigm 2).
Results: We observed a peak average decrease in V_S/f_p of $25 \pm 15\%$ in cortical regions ($t = 3.2$, $p = 0.03$), $15 \pm 11\%$ in thalamus ($t = 2.8$, $p = 0.05$), $16 \pm 14\%$ in striatum ($t = 2.6$, $p = 0.06$), and $35 \pm 34\%$ in cerebellum ($t = 2.8$, $p = 0.05$). This effect reflected a combination of a significant decrease in tissue concentration of 5-IA (7-16% region specific, $p < 0.05$) and a significant increase in plasma parent concentration (8%, $p < 0.05$). There were no significant changes in subjects' self-reported mood symptoms after physostigmine challenge.
Conclusions: We developed a paradigm to interrogate the cholinergic system *in vivo* in human subjects and observed a significant decrease in specific binding of [^{123}I]5-IA following physostigmine challenge, consistent with an increase in endogenous extracellular ACh levels. This confirms a previous study in baboons (Fujita et al. 2003). This imaging tool may have enormous potential to facilitate the development of innovative medicines aimed at modulating the cholinergic system. This study is inherently innovative in the use of neuroreceptor imaging techniques to interrogate the ACh system *in vivo* in human subjects. **1.** Fujita M, Al-Tikriti M, Tamagnan G, et al. Influence of acetylcholine levels on the binding of a SPECT nicotinic acetylcholine receptor ligand [123I]5-I-A-85380. *Synapse.* 2003;48:116-122. **2.** Esterlis I, Cosgrove K, Batis J, et al. Quantification of smoking induced occupancy of β2-nicotinic acetylcholine receptors: estimation of nondisplaceable binding. *Journal of Nuclear Medicine.* 2010;51:1226-1233.
Keywords: acetylcholine, beta2-nAChR, SPECT, physostigmine, mood
Disclosure: I. Esterlis, Nothing to Disclose; J. Hannestad, Nothing to Disclose; F. Bois, Nothing to Disclose; A. Sewell, Nothing to Disclose; R. Tyndale, **Part 1:** Tyndale has participated in one day advisory meetings for Novartis and McNeil; J. Seibyl, **Part 1:** Seibyl has equity interest in Molecular Neuroimaging, LLC; M. Picciotto, Nothing to Disclose; J. Krystal, **Part 1:** Consultant Note: The Individual Consultant Agreements listed below are less than $10,000 per year, Aisling Capital, LLC, Astellas Pharma Global Development, Inc., AstraZeneca Pharmaceuticals, Biocortech, Brintnall & Nicolini, Inc., Easton Associates, Gilead Sciences, Inc., GlaxoSmithKline, Janssen Pharmaceuticals, Lundbeck Research USA, Medivation, Inc., Merz Pharmaceuticals, MK Medical Communications, F. Hoffmann-La Roche Ltd, Sage Therapeutics, Inc., SK Holdings Co., Ltd, Sunovion Pharmaceuticals, Inc., Takeda Industries, Teva Pharmaceutical Industries, Ltd., **Part 2:** Editor - Biological Psychiatry; M. Laruelle, **Part 1:** Laruelle was a consultant for Amgen, Pfizer and Roche and a GSK shareholder at the time of completion of this study and is now a full time employee of UCB Pharma; R. Carson, Nothing to Disclose; K. Cosgrove, Nothing to Disclose.

T75. Neurobiological Differences in Mentalization in Anorexia Nervosa

Carrie J. McAdams*, Daniel C. Krawczyk, Graham Emslie

UT Southwestern Medical Center, Dallas, Texas

Background: Anorexia nervosa has been associated with poor performance on tasks requiring understanding other people's thoughts and feelings: a social cognitive process also termed

mentalization. Using functional MRI, neural regions typically engaged by mentalization have been identified in healthy people, and include the cingulate, precuneus, temporoparietal junctions, the medial frontal gyri, and the inferior frontal gyri.
Methods: We compared fMRI activations in 17 women recovering from anorexia (RAN) and 17 healthy women (CON) using two fMRI tasks eliciting mentalization. The Attribution task compared responses to animated shapes considered either as having a social relationship (*People: All Friends?*) or a physical relationship (*Bumper Cars: Same Weight?*). The Appraisal task examined fMRI activations while the subject evaluated the validity of personalized statements (*Self*, "I believe I am kind; *Reflected*, "My friend believes I am dependable").
Results: We used whole-brain, voxel-wise two-sample *t*-tests to compare activity associated with mentalization in the CON and RAN groups. The right temporoparietal junction (RTPJ, $p_{unc} < 0.001$, 94 voxels) showed decreased activation in the RAN group compared to the CON group in the *People – Bumper* contrast of the Attribution task. In the Appraisal task, the *Reflected – Self* contrast showed differences in activation of the dorsal anterior cingulate (dACC, $p_{unc} < 0.001$, 379 voxels).
Conclusions: Both the RTPJ and the dACC have been closely tied to social evaluative processes in healthy individuals. We observed that RAN subjects showed different neural activations than CON subjects during both impersonal (RTPJ, Attribution) and personalized (dACC, Appraisal) mentalization tasks. These data suggest biological factors may be involved in problems related to social cognitive processing in anorexia nervosa.
Keywords: social cognition anorexia nervosa neuroimaging eating disorders mentalization
Disclosure: C. McAdams, Nothing to Disclose; D. Krawczyk, Nothing to Disclose; G. Emslie, **Part 1:** Consultant, BioBehavioral Diagnostic Company, Bristol-Myers Squibb Company, Eli Lilly, INC Research, Inc., Lundbeck, Pfizer, Seaside Therapeutics, Shire, Valeant, Wyeth, Research Support, BioMarin, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Somerset, Speakers Bureau, Forest Laboratories, **Part 4:** BioMarin, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Somerset.

T76. Neural and Behavioral Markers of Treatment Response in PTSD: A Longitudinal fMRI Study

Yuval Neria*, Gregory M. Sullivan, Erel Shvil, Scott Schafer, Mariana Neria, Miriam Campeas, John C. Markowitz, Tor D. Wager, Mohammed R. Milad

Columbia University, New York, New York

Background: A central feature of posttraumatic stress disorder (PTSD) is a failure to attenuate learned fear responses to trauma-associated stimuli. Translational work has suggested a deficiency in the memory of fear extinction in PTSD, which is associated with aberrant functional activation of nodes of the fear extinction network involving ventromedial prefrontal cortex (vmPFC), amygdala, and hippocampus (Milad et al, 2009; Shin et al, 2005). Prolonged Exposure (PE) therapy, currently among the most efficacious for PTSD, involves enhancement of extinction learning. To advance identification of biomarkers of treatment response in PTSD, we employed fMRI to examine whether PE treatment is associated with beneficial changes in recall of extinction and its neural correlates. The study is ongoing.
Methods: Nineteen PTSD patients (7 male, 12 female; age 39.4 yrs) and 15 trauma-exposed healthy controls (TE-HCs; 7 male, 8 female; age 35.3 yrs) have completed baseline; and 10 PTSD and 8 TE-HCs have completed follow-up (post 10 wks). Using a 2-day fear conditioning/extinction task (Milad et al., 2007) during fMRI, extinction recall deficits were quantified by skin conductance response (SCR). On Day 1, subjects were *conditioned* to 2 conditioned stimuli (CS+: red and blue lights) paired with an aversive unconditioned stimulus (US), a mild shock, in "fear" context; a 3rd light (yellow) was also presented, never followed by shock (CS-). Learned fear was *extinguished* by repeated presentation of only 1 of the 2 CS+'s (without US reinforcement) in "safe" context. On Day 2, extinction *recall* was assessed by presentation of all 3 lights: extinguished CS+ (CS+E); CS+ not extinguished (CS+NE); and CS-, all presented in "safe" context. Ten weeks later, PTSD and TE-HCs repeated the same procedures after PTSD subjects completed 10 weeks of PE therapy.
Results: 1) Baseline: a) Fear Conditioning: Significant Stimulus main effect, $F = 36.95$, $p < 0.001$, with greater response to the CS+ (first 4 to-be CS+E and to-be CS+NE trials) than to the CS- among both the PTSD and TE-HC groups. No significant Group main effect or Group x Stimulus interaction was found, suggesting the PTSD and TE-HC groups had similarly conditioned to the CS+. b) Extinction Learning: No significant main effect of Stimulus, Group or Group x Stimulus interaction (last 12 CS+ vs. last 12 CS- trials), suggesting comparable extinction learning had been achieved in both groups. c) Extinction Recall: No significant main effect of Stimulus, Group or Group x Stimulus interaction (first 4 trials CS+E vs. first 4 trials CS+NE). Extinction retention index was smaller in PTSD than in TE-HCs (36% vs. 70%). D) Brain Correlates of Extinction Recall: Lesser activation in bilateral vmPFC and right insula in PTSD compared to TE-HC subjects in response to the CS+E vs. CS+NE during early recall. 2) Post Treatment a) Fear Conditioning: Significant Stimulus main effect ($F = 21.94$, $p = <.001$), with greater responses to CS+ than CS- in both PTSD (.10 ± .09 ms vs. -.05 ± .10 ms) and TE-HC groups (1.00 ± .29 ms vs. .25 ± .10 ms). There was a significant Group main effect ($F = 9.75$, $p = .007$), as well as a significant Group x Stimulus interaction ($F = 11.1$, $p = .005$). b) Fear Extinction: No significant main effect of Stimulus, Group or Group x Stimulus interaction. c) Extinction Recall: Significant Stimulus main effect ($F = 7.31$, $p = .017$) and significant Group x Stimulus interaction ($F = 16.25$, $p = .001$), but no significant group effect ($F = 3.93$, $p = .067$). Whereas the TE-HC group exhibited smaller SCRs to the stimulus extinguished during the previous extinction learning phase compared with the stimulus that had not been extinguished (.13 ± .09 ms for CS+E vs. .47 ± .17 ms), the PTSD group did not (.12 ± .05 ms vs. .05 ± .05 ms), suggesting impaired recall in the PTSD group. 3) Pre-Post treatment behavioral and fMRI Changes. Extinction Index increased in PTSD patients from 36% to 73%. While the fMRI data showed no differences between PTSD and TE-HCs during extinction recall on *a priori* regions of interests, it did show a significant within group difference in the PTSD group in both vmPFC and left hippocampus comparing baseline to post-treatment. Specifically, while vmPFC showed hypoactivation when comparing BOLD contrasts (CS+E vs. CS+NE) at baseline, during post treatment assessment it showed hyperactivation. The left hippocampus, which showed mild activation at baseline, had significantly increased activation post PE therapy. Moreover within the PTSD group, treatment responders (≥50% reduction in CAPS score) were distinguished from non-responders by greater activation in vmPFC and left hippocampus.
Conclusions: Our findings suggest that PTSD is associated with extinction recall deficits and dysfunctional activation of key fear circuitry structures such as vmPFC and hippocampus (Milad et al., 2009), providing further evidence that PTSD is a disorder of "deficient recovery" (Neria & Sullivan, 2011). Our data suggest for the first time that extinction-focused therapies such as PE may be especially beneficial in improving extinction capacities in PTSD and normalizing dysfunctional activation in associated brain regions in the subset responders to PE. Taken together, our findings highlight the advantages of treatment approaches, which focus on improving pathological function within fear circuitry.
Keywords: PTSD; Fear Circuitry; fMRI; Prolonged Exposure; Fear Extinction
Disclosure: Y. Neria, Nothing to Disclose; G. Sullivan, Nothing to Disclose; E. Shvil, Nothing to Disclose; S. Schafer, Nothing to Disclose; M. Neria, Nothing to Disclose; M. Campeas, Nothing to Disclose; J. Markowitz, Nothing to Disclose; T. Wager, Nothing to Disclose; M. Milad, Nothing to Disclose.

T77. Prefrontal Brain Activity Predicted by Dopaminergic Genes in Healthy Adults is Modulated by Antipsychotics in Schizophrenia

Thomas Weickert*, Ans Vercammen, Ashley Skilleter, Rhoshel Lenroot, Cynthia S. Weickert

University of New South Wales, Randwick, Australia

Background: The dopamine system plays a crucial role in mediating cognitive and affective processes. Aberrant dopamine neurotransmission is also thought to underlie the symptoms of schizophrenia. Dopamine-dependent prefrontal response relies on the regulation of both dopamine availability and the relative balance of D1/D2 receptor mediated action. Thus, the combined effect of genetic variability in catechol-O-methyltransferase (COMT) and dopamine D2 receptor (DRD2) is expected to bias cortical responses and behavior. The current study aimed to determine the extent to which two common functional genetic variants, the COMT val$^{108/158}$met (rs4680) and DRD2 G-T (rs2283265) polymorphisms, combine additively to determine prefrontal brain activity during cognitive-affective processing in healthy people and in schizophrenia. We predicted that inheritance of a greater number of prefrontal risk alleles will be associated with relatively reduced prefrontal activity in healthy people, producing prefrontal hypoactivity similar to that reported in schizophrenia. Also, due to DRD2 antagonism produced by antipsychotics, the relative influence of genetic variability through combined COMT and DRD2 polymorphisms on prefrontal activity may be obscured in schizophrenia.
Methods: Forty-three healthy adults and twenty-seven people with schizophrenia received an fMRI scan while completing an emotional response inhibition test in which participants suppressed responses to words associated with negative emotions in a go/no-go paradigm. Whole brain analysis in the group of healthy adults revealed seven clusters showing increased activation during the inhibition of responses to negative words, which were defined as regions-of-interest (ROIs) for further analysis. Blood samples were collected and DNA was genotyped using Taqman SNP assays. The number of "risk" alleles was tallied in each participant to generate an oligogenic score, which we used as a predictor of brain activation. We also tested whether task related brain activity was related to antipsychotic dosage in schizophrenia.
Results: People with schizophrenia showed a significantly reduced brain activity during inhibition of responses to negative words in left insula ($F_{1,64} = 5.72$, $p = .02$), left BA 10 ($F_{1,64} = 5.92$, $p = .02$), right BA 10 ($F_{1,64} = 8.59$, $p = .005$), right ACC ($F_{1,64} = 6.12$, $p = .02$), and right BA 9 ($F_{1,64} = 6.99$, $p = .01$) compared to healthy adults. As predicted, during inhibition of responses to negative words we detected a significant linear association between increasing prefrontal dopamine risk allele load and reduced activation in the left insula (beta $= -.45$, $t_{39} = -3.12$, $p = .003$), left BA10 (beta $= -.47$, $t_{39} = -3.28$, $p = .002$), right BA10 (beta $= -.43$, $t_{39} = -2.98$, $p = .005$), right SMA (beta $= -.31$, $t_{39} = -2.05$, $p = .047$) and right BA9 (beta $= -.37$, $t_{39} = -2.52$, $p = .016$) in healthy adults. We found no relationship between dopamine risk allele load and brain activation in schizophrenia (all regions p's $> .3$). We observed a negative association between daily chlorpromazine equivalent dose and dorsolateral prefrontal activation during inhibition of response to negative words (right BA 9: beta $= -.42$, $t_{25} = -2.27$, $p = .03$) in schizophrenia.
Conclusions: These results provide the first evidence that genetic variation controlling D2 receptor characteristics and synaptic dopaminergic availability combine to shape neural responses of the prefrontal cortex during cognitive-affective challenges and that common genetic variation influences schizophrenia endophenotypes through small but additive effects. Our data in healthy people suggest that availability of dopamine acting through postsynaptic dopamine D2 receptors makes robust contributions to task-related activation of prefrontal neurons. The allele dose effect on prefrontal cortex activation was not seen in people with schizophrenia receiving antipsychotics. Antipsychotics could be considered an overriding environmental factor which obscures underlying dopaminergic genetic effects in schizophrenia, rendering them non-penetrant. This suggests that prefrontal hypofrontality, commonly found in schizophrenia, potentially has at least two sources: first, inheritance of risk genes biasing the prefrontal cortex to be underactive under conditions of cognitive emotional challenge and second, as a consequence of DRD2 blockade. Thus, dopaminergic genes additively combine in healthy people to produce the hypofrontality endophenotype characteristic of schizophrenia. Genetic effects are obscured by antipsychotics which do not normalize cortical function.
Keywords: schizophrenia dopamine D2 receptor catechol-O-methyltransferase prefrontal cortex emotional inhibition antipsychotics
Disclosure: T. Weickert, Nothing to Disclose; A. Vercammen, Nothing to Disclose; A. Skilleter, Nothing to Disclose; R. Lenroot, Nothing to Disclose; C. Weickert, Nothing to Disclose.

T78. Neural Changes Associated with Attention Bias Modification Treatment: Implications for Anxiety Disorders

Jennifer Britton*, Jenna Suway, Michelle Clementi, Yair Bar-Haim, Nathan Fox, Daniel S. Pine

University of Miami, Coral Gables, Florida

Background: Attention Bias Modification Treatment (ABMT) is emerging as a possible treatment for anxiety disorders. Individuals with anxiety disorders often have attention biases towards threat and neural perturbations in regions associated with threat salience and attentional control. Novel behavioral therapies, focused specifically on attention-training, might target these underlying neural perturbations and provide therapeutic benefit. Therefore, it is important to understand the behavioral and neural changes following active attention training compared to placebo training.
Methods: Healthy adults who were between 18-30 years old and highly socially anxious (i.e., scored $\geqslant 50$ on Liebowitz Social Anxiety Scale, LSAS) were recruited for this study. Participants were pseudo-randomly assigned to an active training group ($n = 26$) or placebo training group ($n = 27$). However, only a subset of these 53 subjects completed brain imaging. The active training task was designed to train participants to attend away from threat. Participants completed both acute and extended training. Acute attention bias training was completed in a 3T MRI scanner. Extended training sessions were completed outside of the scanner (i.e., twice weekly over a 4-week period). Using the dot-probe task, attention biases were measured in the scanner before and after acute training and after extended training. In the dot-probe task, individuals detect a probe following a threat-neutral stimulus pair. In congruent trials, the probe appears in the location the threatening stimulus (i.e., angry face) occupied. In incongruent trials, the probe appears in the opposite location. Attention bias is measured using the difference in reaction time to these two trials. Changes in attention biases ($n = 19$/group) and neural activation ($n = 15$/group) were examined in a subset of the 53 subjects initially entering the study. Pre-processing and whole-brain analyses were conducted in AFNI. Group (Active, Placebo) $\times$ Time(Baseline, after extended training) $\times$ Condition(Congruent, Incongruent, Neutral) interactions were tested using GroupAna and an equivalent $p < 0.05$ corrected threshold. Interactions were decomposed after extracting data from functionally-defined regions.
Results: Neither training group had a significant attention bias towards or away from threat at baseline [both $p > 0.8$]. Although a Group-Time $\times$ Condition interaction was not significant [$p > 0.5$], the active training group exhibited an attention bias away from threat after extended training [$t(18) = -2.1$, $p < 0.05$]. Contrary to the behavioral results, interaction effects were detected following extended training in several brain regions, including the left rostral anterior cingulate (rACC) [(-9, 44, -1), $F = 7.0$, $k = 15$ voxels] and amygdala [right: (19,4, -24), $F = 6.9$, $k = 128$ voxels; left (-19,1, -11), $F = 11.1$, $k = 106$ voxels]. The active group showed increased left rACC activation in

response to incongruent trials, the trial to which they had been trained to attend, [$p<0.04$], while the placebo group showed increased activation in response to the congruent trials [$p<0.05$]. The placebo group showed increased bilateral amygdala activation in response to the congruent trials [both $p<0.008$] and decreased right amygdala activation to the incongruent trials [$p<0.04$]. No changes were detected in response to the neutral condition in either group [all $p>0.1$].
Conclusions: Changes in neural activation were primarily detected in the placebo group. Although unexpected, this result could reflect increased neural stability in attention control in the active group; whereas, exposure to threatening stimulus without active training may result in heightened threat sensitivity.
Keywords: anxiety, attention, training, fMRI
Disclosure: J. Britton, Nothing to Disclose; J. Suway, Nothing to Disclose; M. Clementi, Nothing to Disclose; Y. Bar-Haim, Nothing to Disclose; N. Fox, Nothing to Disclose; D. Pine, Nothing to Disclose.

T79. Effects of Nicotine and Cannabis Use on Structural Connectivity in Brain's Reward-Motivation Circuitry

Francesca M. Filbey*, Sina Aslan, Arvind Caprihan, Judith Segall, Vincent Calhoun

University of Texas at Dallas, Dallas, Texas

Background: Symptoms of nicotine and cannabis use disorders have been linked to aberrant neurocognitive activity particularly within reward and motivation systems. At present, however, the mechanisms that underlie these abnormalities in brain network function remain poorly understood. The emerging literature suggests potential associations with abnormalities in structural connectivity as assessed by tractography and fractional anisotropy (FA) analysis of white matter via diffusion tensor imaging (DTI) MRI.
Methods: DTI scans were collected via 3T Siemens whole body scanner on 62 control (*M* age = 30.0, 39 males), 58 nicotine (*M* age = 30.2, 33 males) and 49 cannabis (*M* age = 28.3, 33 males) users. Histogram and tractography analyses were performed to assess global and white matter fiber tract-based FA, respectively.
Results: The global FA of nicotine and cannabis groups was significantly different from the control group (Control = 0.478, Nicotine = 0.489, Cannabis = 0.491; $p<0.005$). Moreover, the cannabis group's distribution of voxels across different FA ranges (i.e., histogram characteristics) was significantly different from the control group as measured by kurtosis ($p=0.02$), skewness ($p=0.02$), and full width half maximum ($p=0.06$). Closer examination of these differences was performed by examining FA in three *a priori* fiber tracts within the reward and motivation systems: bilateral cingulum, bilateral uncinate fasciculus, and bilateral hippocampal part of the cingulum. One-way ANOVA comparisons showed significant differences between the groups. Post-hoc analyses revealed higher FA in the following fiber tracts in the nicotine and cannabis groups compared to the control group: left cingulum ($p=0.004$), right cingulum ($p=0.002$), right hippocampal cingulum part ($p=0.046$) and left uncinate fasciculus fiber tracts ($p<0.001$). Lastly, we determined how white matter integrity is associated with symptoms of nicotine and cannabis use disorders via correlation analyses. The results showed that for the nicotine group, Fagerstrom Test for Nicotine Dependence (FTND) scores were correlated negatively with the FA of right cingulate ($r=-0.27$, $p=0.04$), left cingulum-hippocampal-part ($r=-0.33$, $p=0.01$), left uncinate ($r=-0.27$, $p=0.04$) and right uncinate fasciculi ($r=-0.39$, $p=0.003$) such that the greater the tobacco dependence severity, the less white matter integrity in these fiber tracts. In the cannabis group, frequency of marijuana use correlated positively with the FA of left uncinate fasciculus ($r=0.43$, $p=0.004$) suggesting that greater cannabis use is associated with increased white matter integrity in this fiber tract.
Conclusions: These findings suggest that while there is greater global FA in both regular nicotine and cannabis using groups compared to non-users, FA is differentially associated with cannabis and nicotine use suggesting that fiber tracts other than the uncinate fasciculus, cingulum, and hippocampal part of the cingulum may be associated with severity of nicotine dependence. To conclude, white matter abnormalities within reward-motivation networks may be the underlying mechanism related to neurocognitive changes in cannabis use disorders.
Keywords: Cannabis, tobacco, DTI, white matter, connectivity
Disclosure: F. Filbey, Nothing to Disclose; S. Aslan, Nothing to Disclose; A. Caprihan, Nothing to Disclose; J. Segall, Nothing to Disclose; V. Calhoun, Nothing to Disclose.

T80. Longitudinal Assessment of Neurochemical Changes in First-episode Mania Following Lithium Treatment: An Interim MRS Analysis from the Bipolar Disorder Imaging and Treatment Research Center

David E. Fleck*, Wen-Jang Chu, Richard Komoraski, James Eliassen, Jing-Huei Lee, Matthew Norris, Michael Cerullo, Caleb Adler, Melissa DelBello, Stephen Strakowski

University of Cincinnati, Cincinnati, Ohio

Background: Proton (^{1}H) magnetic resonance spectroscopy (MRS) studies in manic patients with bipolar disorder (BD) suggest that glutamate (Glu) concentrations are elevated within anterior-limbic brain structures. Since Glu is the predominant excitatory neurotransmitter, excessive glutamatergic activity may underlie increased anterior-limbic metabolism in mania. Repeated increases in excitatory neurotransmission may cause glutamatergic neurotoxicity, thereby initiating neuroanatomic and neurophysiologic changes. It is not known whether standard treatments for BPD prevent these changes. Lithium is the only medication that has efficacy primarily in mania. Lithium inhibits inositol monophosphatase, leading to decreases in inositol, which may underlie its therapeutic action. Perhaps by decreasing excitatory glutamatergic neurotransmission through this mechanism of action, lithium corrects anterior-limbic hypermetabolism and diminishes the risk of neurotoxicity, thereby preventing disease progression. Studies of early course patients, prior to significant disease progression, are needed to address these possibilities. With these considerations in mind, we conducted an interim analysis of data from the University of Cincinnati Bipolar Disorder Imaging and Treatment Research Center to identify *myo*-Inositol (mI) and Glu abnormalities near the onset of BD, and then determine how these abnormalities change in response to lithium treatment. We examined ^{1}H-MRS in first-episode patients with bipolar mania at Baseline, Week 1, and Week 8 post-lithium treatment. Measurements were contrasted with those made at the same intervals in healthy comparison (HC) participants. We predicted that (1) compared with the HC group, at baseline the BD group would exhibit elevated Glu, which would normalize in treatment responders by Week 8, and (2) consistent with its mechanism of action, lithium responders would exhibit significant decreases in mI at Week 1.
Methods: Fourteen adult manic participants with BD and 25 demographically-matched HC participants received a resting-state MRS scan on a 4-Tesla MRI scanner. All BD participants received lithium for eight weeks as part of a medication trial with an active control, at which time they were classified as either responders ($n=8$) or non-responders ($n=6$). For this preliminary analysis response was defined liberally as YMRS $\leqslant$ 10 and CGI $\leqslant$ 3 at Week 8 to best equate the groups. ^{1}H-MRS was obtained immediately following two fMRI acquisitions to be used in the final analysis and reported separately. Voxels were positioned to encompass left and right ventrolateral prefrontal cortex (VLPFC) and midline anterior cingulate cortex (ACC) and data were acquired using single-voxel PRESS sequences (voxel size = 8cc, TR = 2000 ms, TE = 23 ms, 128 averages). The localized PRESS spectra were curve fitted using LCModel software with eddy current correction and absolute concentrations of Glu and mI metabolites were determined with an internal water reference. Each metabolite was analyzed separately at each of the three voxel locations

using a 3 (Responder, Non-Responder, Control) x 3 (Baseline, Week 1, Week 8) mixed ANOVA.
Results: For the Glu analysis, concentrations in VLPFC differed across Time as a function of Response group. This impression was confirmed by a highly significant interaction of Response x Time [$F(4,72) = 4.07$, $p = 0.005$]. The interaction resulted primarily from significantly increased Glu concentrations in lithium responders at Baseline vs. Week 1 [5.0 ± 0.7 vs. 6.0 ± 0.5; $t(7) = -3.23$, $p = 0.01$ after Bonferroni correction] and Baseline vs. Week 8 [5.0 ± 0.7 vs. 6.1 ± 1.3; $t(7) = -3.05$, $p = 0.01$ after Bonferroni correction]. No mI analysis was significant at any voxel location. Measurements across Baseline (5.7 ± 1.0), Week 1 (5.3 ± 1.2), and Week 3 (5.3 ± 0.9) in the HC group provided evidence of measurement stability ($p > 0.05$).
Conclusions: Our aim was to identify neurochemical abnormalities near the onset of BD, prior to significant disease progression, and then determine how these abnormalities change in response to lithium treatment. Lithium was chosen as the treatment because it is an effective antimanic agent, yet likely involves a distinct mechanism of action. Our stated hypotheses were not confirmed in this interim analysis. Indeed, we identified similar Glu concentrations in left VLPFC at baseline that significantly increased by Week 1 and stabilized at a high level through Week 8. Although contrary to our prediction, elevated Glu in left VLPFC in response to lithium treatment may be a potential neurochemical marker. Further research will be needed to uncover the mechanisms underlying this effect, determine its ultimate reliability as a biomarker, and examine whether it is observed in chronically ill patients as well. In the final report of this work, we will extend these findings by including potential covariates that were not considered in the present analysis and compare lithium responders with atypical antipsychotic responders using a broader spectrum of metabolites. Despite the preliminary nature of this work, Glu may provide a signal of lithium treatment response in acute mania with potential to predict response for future studies.
Keywords: Bipolar Disorder, Glutamate, Lithium, Magnetic Resonance Spectroscopy, Neuroimaging
Disclosure: D. Fleck, Nothing to Disclose; W. Chu, Nothing to Disclose; R. Komoraski, Nothing to Disclose; J. Eliassen, Nothing to Disclose; J. Lee, Nothing to Disclose; M. Norris, Nothing to Disclose; M. Cerullo, Nothing to Disclose; C. Adler, **Part 1:** AstraZeneca, Eli Lilly, Pfizer, Otsuka, Forest, Sunovion, Novartis, Glaxo Smith-Kline, Amylin, Merck, **Part 4:** AstraZeneca, Eli Lilly, Pfizer, Otsuka, Forest, Sunovion, Novartis, Glaxo Smith-Kline, Amylin; M. DelBello, **Part 1:** AstraZeneca, Eli Lilly, Johnson and Johnson, Janssen, Pfizer, Otsuka, Sumitomo, NIDA, NIMH, NIAAA, NARSAD, GlaxoSmithKline, Merck, Novartis, Lundbeck, Bristol-Myers Squibb, Schering-Plough, **Part 4:** AstraZeneca, Eli Lilly, Johnson and Johnson, Janssen, Pfizer, Otsuka, Sumitomo, NIDA, NIMH, NIAAA, NARSAD, GlaxoSmithKline, Merck, Novartis, Lundbeck; S. Strakowski, **Part 1:** NIMH, Janssen, Eli Lilly, Janssen/J&J, AstraZeneca, Sumatomo, Pfizer, NIDA, NIAAA, NIMH, NARSAD, University of Utah, Johns Hopkins University, University of Nebraska, Web MD, **Part 4:** NIMH, Janssen, Eli Lilly, Janssen/J&J, AstraZeneca, Sumatomo, Pfizer, NIDA, NIAAA, NIMH, NARSAD.

T81. White Matter Abnormalities in Skin Picking Disorder: A Diffusion Tensor Imaging Study

Jon E. Grant*, Brian L. Odlaug, Samuel R. Chamberlain, Adam Hampshire

University of Chicago, Chicago, Illinois

Background: Skin picking disorder (SPD) is characterized by the repetitive and compulsive picking of skin resulting in tissue damage. The nosological status of SPD and its relationship with other Axis I disorders remains unclear, and one critical means of attempting to understand SPD and its relationship with other disorders is by identifying neural circuitry involved in its pathophysiology. The aim of this study was to assess the integrity of white matter tracts in subjects with SPD compared with healthy control subjects. In particular, we sought to conduct an analysis across all white matter tracts within the brain using diffusion tensor imaging (DTI) alongside recently validated and statistically powerful methods of permutation cluster analysis to ensure stringent corrections for multiple comparisons. It was hypothesized that SPD would be associated with disorganized white matter tracts, i.e., reduced fractional anisotropy (FA), in similar regions to those previously identified as being abnormal in trichotillomania: namely, tracts involving the bilateral orbitofrontal cortex and anterior cingulate cortices, the left pre-supplementary motor area, and the left temporal lobe.
Methods: Thirteen volunteers meeting *DSM-5* criteria for skin picking disorder, and free from other psychiatric disorders, and 12 healthy, age and gender matched, control subjects underwent MRI scans using a 3.0-T system. Skin picking severity was assessed using the Yale Brown Obsessive Compulsive Scale modified for Neurotic Excoriation (NE-YBOCS). Voxelwise statistical analysis of the imaging data was carried out using TBSS (Tract-Based Spatial Statistics), which is part of the FSL software package. FA images were firstly created by fitting a tensor model to the raw diffusion data using FDT, and then extracting brain data using BET. All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT –this uses a b-spline representation of the registration warp field. The mean FA image was then created and thinned to create a mean FA skeleton, which represents the centres of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton and fed forward into voxelwise cross-subject statistics. Cross-group contrasts were generated using permutation modelling with the FSL Randomise toolbox. The resultant statistical images were rendered with cluster correction for the entire search volume using Threshold-Free Cluster Enhancement at $p < 0.05$.
Results: Thirteen subjects (mean age 26 SD = 5.5) with SPD and 12 age-matched control subjects (mean age 26 SD = 6.4) met inclusion criteria and underwent imaging. No clinically significant MRI structural abnormalities were identified in any subjects. The groups did not differ significantly in terms of age, sex, IQ, or handedness. The group with SPD as compared with control subjects showed abnormally reduced FA in distributed white matter tracts connecting the orbitofrontal cortex and anterior cingulate cortices bilaterally.
Conclusions: The current data implicate dysconnectivity in white matter tracts connecting neural regions involved in motor generation and suppression, along with affective regulation, in the pathophysiology of skin picking disorder.
Keywords: imaging, grooming, impulsivity, white matter, dermatology
Disclosure: J. Grant, **Part 1:** Research grant support from Psyadon Pharmaceuticals, Transept Pharmaceuticals, and Forest Pharmaecuticals, **Part 4:** Research grant support from Psyadon Pharmaceuticals, Transept Pharmaceuticals, and Forest Pharmaecuticals; B. Odlaug, Nothing to Disclose; S. Chamberlain, **Part 1:** Consultant for Cambridge Cognition, Eli Lilly, Shire, and P 1 Vital, **Part 2:** Consulting to Cambridge Cognition and P1 Vital, **Part 3:** Consulting to Cambridge Cognition and P1 Vital; A. Hampshire, Nothing to Disclose.

T82. Dopaminergic Networks: Brain Maturation and ADHD

Dardo Tomasi*, Nora D. Volkow

NIAAA/NIH, Upton, New York

Background: Developmental changes in dopaminergic networks likely contribute to the dramatic increase in risk-taking behaviors and the emergence of various psychiatric disorders in the transition from childhood into adolescence. Several PET studies documented a significant decline in DA neurotransmission (receptors, transporters, DA synthesis) with age but the use of radioactive tracers precludes their application to the study of healthy children. Here we use "resting-state" functional connectivity (RFC) measures derived from seeds in VTA and SN (main DA nuclei) to study changes in DA neurotransmission in the transition from childhood to adulthood. Our

working hypothesis was that typically developing children (TDC) and healthy adults would show differential midbrain connectivity in regions of the nigrostriatal, mesolimbic and mesocortical DA pathways. In order to assess the sensitivity of these pathways to developmental disorders we also evaluated the connectivity of VTA and SN in ADHD children and tested the "delayed maturation" hypothesis in ADHD.
Methods: A total of 1420 open-access "resting-state" magnetic resonance imaging datasets were included: 247 ADHD (12 ± 3 years old; 197 boys) and 459 TDC (12 ± 3 years old; 244 boys) from the "ADHD-200" initiative and 714 (23 ± 3 years old; 321 males) healthy adults from the "1000 functional connectomes" project. After standard image preprocessing steps (realignment, removal of motion-related and global signal fluctuations, spatial normalization), seed-voxel correlation with Gram-Schmidt orthogonalization was used to compute the VTA and SN connectivity patterns. Voxelwise ANOVA (with age, gender and mean motion covariates) with a conservative statistical threshold ($P_{FWE} < 0.05$, family-wise error corrected for multiple comparisons in whole brain) was used to evaluate the statistical significance of group differences in functional connectivity.
Results: TDC demonstrated lower VTA-connectivity in left NAc, amygdala, hippocampus, parahippocampus, vermis, insula, PFC, ACC, OFC, SMA, temporal pole and middle temporal cortex, but higher VTA-connectivity in subthalamic nucleus and thalamus than adults. TDC demonstrated higher SN-connectivity than adults in NAc, amygdala, hippocampus, parahippocampus, insula, subthalamic nucleus, globus pallidus, vermis, temporal pole, anterior and middle cingulum, PFC, OFC, SMA, and Rolandic operculum. Voxelwise SPM correlations revealed significant age-related VTA-connectivity increases in NAc, caudate, vermis, insula, DMN and temporal pole. Age-related SN-connectivity decreases were significant in caudate, motor and premotor cortices, temporal pole, Rolandic operculum, occipital cortex, and postcentral gyrus. ADHD children had higher VTA-connectivity in amygdala, hippocampus, globus pallidus, thalamus, vermis and insula, and higher SN-connectivity in amygdala and insula than TDC. A delayed maturation was found in thalamus, subthalamic nucleus and globus pallidus (VTA-connectivity), left amygdala and insula (SN-connectivity) and accelerated maturation in hippocampus, amygdala, vermis, left caudate, right NAc and right insula (VTA-connectivity) in ADHD children compared to TDC.
Conclusions: Here we identify overlapping as well as distinct connectivity patterns for SN and VTA that are consistent with their neuroanatomical projections and with the role of DA in the modulation of brain functional connectivity. We also identify strong connectivity with regions that are not traditionally associated with DA pathways and age-related connectivity changes during childhood/adolescence, as well as prominent differences in functional connectivity between ADHD children and TDC. Overall these findings suggest maturation strengthening of VTA-connectivity with DMN regions and maturation pruning of SN-connectivity with motor and medial temporal cortices during the transition from childhood to adulthood. This transition is characterized by age-related VTA-connectivity increases in limbic and DMN regions and with SN-connectivity decreases in motor and medial temporal cortices. The changes from a predominant influence of SN in childhood/adolescence to a combined influence of SN and VTA in young adulthood might explain the increased vulnerability to psychiatric disorders, such as ADHD, early in life. These findings also demonstrate the feasibility of using RFC and fMRI for studying DA networks in childhood when the increase sensitivity to adverse effects of radioactivity limits the use of PET methods.
Keywords: Dopamine Brain development resting-state functional connectivity ADHD
Disclosure: D. Tomasi, Nothing to Disclose; N. Volkow, Nothing to Disclose.

T83. Odor Modulation during an Alcohol Cue-reactivity Paradigm: A Functional Magnetic Resonance Imaging (fMRI) Preliminary Investigation

Bernadette M. Cortese*, Thomas W. Uhde, Konstantin E. Voronin, Scott Henderson, Joseph P. Schacht, Qing X. Yang, Raymond F. Anton

Medical University of South Carolina, Charleston, South Carolina

Background: Animal and human research suggests emotional state as a contributing factor in alcohol craving and relapse. For example, footshock stress leads to reinstatement of ethanol seeking in rats (Le et al., 1998; Liu & Weiss, 2002, 2003), while negative mood in humans is associated with increased drug craving and post-treatment relapse rates (Cooney et al., 1997; Sinha et al., 2009). Other lines of evidence demonstrate the ability of odors to evoke strong emotions (Ehrlichman & Halpern, 1988; Kiecolt-Glaser et al., 2008). Taken together, the present study was designed to assess the ability of pleasant and unpleasant odors to modulate alcohol cued craving and craving-related brain activation.
Methods: Twenty-two normosmic, non-treatment seeking, alcohol-dependent, young adults (19 Male, 3 Female; mean age 28.0, range 22-39) were systematically presented with several odorants including lavender (LAV), burned rubber (BR), and propylene glycol (PG), an odorless control. Odor hedonics, as well as the degree to which each odor evoked a number of positive and negative emotions, i.e. happy, sad, peaceful, uneasy, and annoyed, were rated on 100 mm visual analog scales. Change scores were calculated for each emotion by subtracting baseline ratings from ratings collected after each odorant presentation. Nineteen of these participants also underwent olfactory fMRI during which either LAV, BR, or PG was delivered concurrently within blocks of alcohol or neutral visual cues in a validated alcohol cue-reactivity task (Myrick et al., 2004). Contrast maps for the alcohol (ALC) blocks minus the neutral beverage (BEV) blocks under the odorless condition (PG) were used as comparisons for ALC- BEV contrasts under the LAV and BR conditions. All fMRI analyses were conducted in FSL.
Results: *Odor and Mood Ratings:* LAV was rated significantly more pleasant ($M = 66.7$, $SD = 22.4$) than BR ($M = 29.1$, $SD = 27.0$, $p < 0.01$, 95% CI = [+17.4, +57.7]), and less disgusting ($M = 9.1$, $SD = 20.4$) than BR ($M = 36.2$, $SD = 33.1$, $p < 0.01$, 95% CI = [-47.9, -6.2]). Both LAV ($M = 49.9$, $SD = 25.0$) and BR ($M = 48.1$, $SD = 24.0$) were rated similar in strength ($p = 1.0$; 95% CI = [-19.3, +22.7]). Change scores (from baseline) revealed a significant mood by odorant interaction, demonstrating the ability of LAV and BR to evoke different emotions ($F_{8,21} = 7.18$, $p < 0.01$). Specifically, LAV induced greater feelings of peacefulness than BR (Mean Difference 29.1, $p < 0.05$; 95% CI = [+1.98, +56.2]) and PG (Mean Difference = 27.7, $p < 0.05$; 95% CI = [+0.57, +54.8]), while BR evoked greater feelings of uneasiness than LAV (Mean Difference 19.8, $p = 0.07$; 95% CI = [-1.04, +40.6]) and PG (Mean Difference 21.4, $p < 0.05$; 95% CI = [+0.59, +42.2]).
Olfactory fMRI: The BOLD response to alcohol cues (ALC minus BEV contrast) during the odorless condition (PG) demonstrated a pattern of activation consistent with previous studies conducted in our laboratory (Myrick et al., 2004) that included significant activation in bilateral striatum, hippocampus, and amygdala, and left accumbens (clusters determined by $Z > 2.3$, corrected cluster threshold $p = 0.05$). This pattern of activity was significantly altered by the presence of burned rubber and lavender. Compared to the odorless condition, BR revealed significant additional activation in bilateral putamen and insula, anterior cingulate, and right accumbens (clusters determined by $Z > 2.3$, corrected cluster threshold $p = 0.05$). In contrast, the LAV condition revealed significantly reduced signal (compared to the odorless condition) in bilateral striatum, hippocampus, amygdala, and accumbens (clusters determined by $Z > 2.3$, corrected cluster threshold $p = 0.05$).
Conclusions: A clear dissociation between the effects of lavender and burned rubber on alcohol-related BOLD response in non-treatment seeking, alcohol-dependent, young adults was demon-

strated in this study. Specifically, alcohol-cued brain activation was amplified during the burned rubber condition and suppressed during the lavender condition. These findings add to the growing evidence demonstrating the ability of odors to influence cognitive processes, while providing new evidence of a potential role for odors in drug cue-reactivity. How lavender and burned rubber modulate the cognitive processing of alcohol cues, including whether odor hedonic value i.e. pleasant versus unpleasant or some other feature of the odors is interacting with alcohol craving, is currently being explored.

Funding: This research was supported by the Charleston Alcohol Research Center (NIAAA- P50 AA010761), NIMH K01 MH090548 (Cortese), and NIAAA K05 AA174353 (Anton).

Keywords: cue-reactivity fMRI odors alcohol dependence craving

Disclosure: B. Cortese, Nothing to Disclose; T. Uhde, Nothing to Disclose; K. Voronin, Nothing to Disclose; S. Henderson, Nothing to Disclose; J. Schacht, Nothing to Disclose; Q. Yang, Nothing to Disclose; R. Anton, **Part 1:** Eli Lilly, Glaxo Smith Kline, Alkermes, Lundbeck, Roche., Schering Plough, Johnson & Johnson, Abbott Laboratories, Merck, Alcomed, **Part 4:** Support from Eli Lilly, Schering Plough, Lundbeck, Alkermes, GlaxoSmithKline, Johnson & Johnson, and Abbott Laboratories as part of the Alcohol Clinical Trials workgroup (ACTIVE). Research contracts/grants from Eli Lilly and Merck. Stockholder in Alcomed which has received STTR support from NIDA.

T84. Brain GABA Levels and Vitamin D3 in Manic Children and Adolescents

Elif Sikoglu, Ana Liso, Debra Starr, Michael Cirillo, Benjamin Nwosu, Ryan Rogan, Martha Castro, Richard Edden, Jean King, David Kennedy, Constance M. Moore*, Jean Frazier

University of Massachusetts Medical School, Worcester, Massachusetts

Background: γ-amino butyric acid (GABA) is the primary inhibitory neurotransmitter in the brain. Significant GABAergic dysfunction is associated with the pathophysiology of Bipolar Disorder (BD) mania, and many medications that are effective in the treatment of BD, may do so through engagement of the GABA neurotransmitter system. In particular, post-mortem studies show decreased GABAergic neuronal density in the Anterior Cingulate Cortex (ACC) of subjects with BD. Using specialized Magnetic Resonance Spectroscopy (MRS) techniques it is possible to measure *in vivo* GABA levels in localized regions of the brain. In recent years it has been suggested that Vitamin D3 meets the criteria for a neuroactive steroid. Vitamin D3 (received through diet or photolysis) is inactive and is converted in the liver to 25-Hydoxy Vitamin D3 (25-OH-D: the main circulating form of the vitamin). 25-OH-D is further converted, in kidney and brain, to 1- α-25-dixydroxy Vitamin D3 (1,25-OH-D: the main biologically active form of Vitamin D3). It has been speculated that 1,25-OH-D may modulate GABA in the brain in a similar fashion to other neuroactive steroids.

The purpose of this pilot study was to investigate ACC GABA and serum 25-OH-D in children and adolescents exhibiting symptoms of mania and in a typically developing comparison (TDC) group & investigate the impact of an 8-week Vitamin D3 supplement on ACC GABA, serum 25-OH-D and mania in youths with mania.

Methods: The Institutional Review Board at the University of Massachusetts Medical School (UMMS) approved this study. All subjects were recruited through the UMMS and online advertising. All of the children were interviewed with the KSADS-PL. Subjects had their manic mood assessed using the Young Mania Rating Scale (YMRS). The Clinical Global Impression - Severity scale (CGI-S) was also used to determine subjects well being at each study visit. The Wechsler Abbreviated Scale of Intelligence (WASI) was used to determine IQ.

Inclusion criteria were male or female, 8 to 17 years. 1) CGI-S $\geqslant$ 3, YMRS $\geqslant$ 15 OR 2) CGI-S $\geqslant$ 3, YMRS $\leqslant$ 14 & $\geqslant$ 8 (and subject has a parent with a diagnosis of BD). Exclusion criteria included: a history of a uncontrolled general medical disorder; a history of neurological illness; autism; schizophrenia; substance dependence; I.Q. $<$ 70. Unique exclusion criteria for TDC included an Axis I diagnosis and a family history of a mood disorder in a first degree relative. Blood was drawn to determine 25-OH-D levels.

^{1}H MRS experiments were conducted using a Philips 3.0 T scanner with MEGA-PRESS to measure the GABA levels. The voxel was placed at the ACC region (18 cm^3). GABA levels were fit using in house software and quantified using the creatine (Cr) peak as reference. Following the baseline assessments manic subjects were provided with a supply of softgel capsules containing 2000 IU Vitamin D3. Subjects are asked to take one softgel daily, orally, at the same time of day, continuing for the duration of the study (8 weeks). If subjects were taking psychotropics, they had been on a stable dose 4 weeks prior to entering the study and maintained that dose for the duration of the study. If subjects were taking a daily multivitamin or vitamin supplement they continued for the duration of the study. Mood was assessed at follow-up Weeks 2, 4, 6 & 8 using YMRS and CGI-S. At the final visit subjects re-did the blood sample and underwent a final MRS scan. Statistical analysis was performed using PAWS Statistics 18.0 for Macintosh OSX using linear regression modeling and repeated measures ANOVA. Results were considered significant for $p < 0.05$.

Results: To date we have enrolled 6 subjects who meet criteria for mania (11.83 ± 2.48 years; 4 male) and 10 TDC (12.40 ± 3.50; 5 male). Using linear regression backward analysis looking at the affect of age, sex and manic status on GABA/Cr showed a trend for GABA/Cr to be higher in manic subjects compared with TDC (0.07 ± 0.01 vs. 0.08 ± 0.02, $p < 0.1$). The age and sex affects on the model were not significant. Using linear regression analysis looking at the affect of manic status on: 1) blood 25-OH-D; 2) YMRS showed: 1) a trend for 25-OH-D to be lower in manic subjects compared with TDC (18.8 ± 6.4 vs. 26.4 ± 9.5, $p < 0.1$); 2) YMRS to be significantly higher in manic subjects compared with TDC (20.8 ± 11.3 vs. 0.3 ± 0.7 $p < 0.000$). In the children with mania, 8 weeks of Vitamin D3 treatment resulted in a trend increase in GABA/Cr (0.07 ± 0.01 vs. 0.08 ± 0.02, $p < 0.1$), a significant increase in 25-OH-D (18.8 ± 6.4 vs. 29.0 ± 9.2, $p < 0.01$), and a significant reduction in YMRS (20.8 ± 11.3 vs. 11.7 ± 9.2, $p < 0.02$).

Conclusions: Children with mania had lower 25-OH-D serum levels compared with TDC. In addition these children with mania also had lower GABA/Cr. One could speculate that the lower neuroactive steroid 1,25-OH-D levels impact the GABAergic system, leading to symptoms of mania. In fact, an 8-week treatment trial with Vitamin D3 significantly reduced manic symptoms, significantly increased 25-OH-D serum levels, and increased GABA/Cr at the trend level. Of note all of the children with mania were determined to be 25-OH-D insufficient at baseline (< 30 ng/ml) compared with half of the TDC (subject recruitment commenced in November 2011 in the Atlantic North East). Things to consider for future studies are the role of 25-OH-D insufficiency in mood symptoms, and the possibility of Vitamin D3 treatments.

Keywords: Vitamin D3, mania, children, GABA, spectroscopy

Disclosure: E. Sikoglu, Nothing to Disclose; A. Liso, Nothing to Disclose; D. Starr, Nothing to Disclose; M. Cirillo, Nothing to Disclose; B. Nwosu, Nothing to Disclose; R. Rogan, Nothing to Disclose; M. Castro, Nothing to Disclose; R. Edden, **Part 1:** I received a one-off speaker honorarium from Eli Lilly; J. King, Nothing to Disclose; D. Kennedy, Nothing to Disclose; C. Moore, Nothing to Disclose; J. Frazier, **Part 4:** Pfizer, Seaside Therapeutics, Roche, GlaxoSmithKline.

85. Altered Activation in Fronto-Striatal Circuits during Sequential Processing in Unmedicated Adults with Obsessive-Compulsive Disorder

Rachel Marsh*, Helen Simpson, Bradley Peterson, Zhishun Wang, Nidhi Parashar, Guillermo Horga

Columbia Unviersity, New York, New York

Background: Obsessive-Compulsive Disorder (OCD) is characterized by intrusive thoughts, images, or impulses (i.e., obsessions) and repetitive acts that are performed to prevent or reduce distress

(i.e., compulsions). Obsessions and compulsions are hypothesized to result from a failure to inhibit or control thoughts and behaviors, respectively. Indeed, neuroimaging evidence suggests that the fronto-striatal circuits supporting self-regulatory capacities are structurally, metabolically, and functionally abnormal in OCD. Most findings implicate the orbitofrontal and anterior cingulate cortices and caudate nucleus in the pathophysiology of OCD. However, self-regulatory capacities involve additional fronto-striatal brain areas that may also be dysfunctional in OCD. Our objective was to examine the functioning of fronto-striatal circuits that support self-regulatory capacities including conflict resolution and sequential processing in unmedicated adults with OCD.
Methods: Twenty-two adults with OCD and 22 healthy, age-matched controls were scanned. The OCD participants were all free of psychotropic medications (14 treatment-naïve and the other 8 had been off an SRI for a mean (SD) of 94 (63) weeks) and any current comorbid Axis I disorder. FMRI scan were acquired during performance of a Simon Spatial Incompatibility task that required ignoring a task-irrelevant feature of a stimulus (the side of the screen on which an arrow appears) when it conflicted with a more task-relevant one (the direction the arrow points). We used general linear modeling to compare the OCD and control groups in their patterns of brain activation during correct responses to conflict-laden stimuli and explore the effects of trial sequence on group differences.
Results: Behavioral performance on the Simon task did not differ between groups. In response to conflict-laden stimuli, OCD participants activated fronto-striatal regions significantly more than controls, specifically a right hemisphere cluster encompassing the putamen, insula and inferior frontal gyrus. Their activation of this cluster was driven not by conflict on a current trial but by their response to the alternation of stimulus congruence (incongruent or congruent) across trial sequences (i.e., current and preceding trials), and was most accentuated in participants with more severe symptoms in the doubt/checking dimension. Functional connectivity from the putamen to other fronto-striatal regions was also greater in the OCD compared to control participants.
Conclusions: When engaging the self-regulatory control necessary to resolve conflict and process alternating stimuli, OCD participants displayed excessive activation in a fronto-striatal circuit that differs from the OFC-ACC-caudate circuit typically implicated in OCD. Dysfunction in this circuit was associated with processing changes in the stimulus context and we speculate that this dysfunction may be related to the cognitive inflexibility typical of persons with OCD.
Keywords: Obsessive-Compulsive Disorder; Self-Regulation; Cognitive Conflict; fMRI; Fronto-striatal circuits
Disclosure: R. Marsh, Nothing to Disclose; H. Simpson, Nothing to Disclose; B. Peterson, Nothing to Disclose; Z. Wang, Nothing to Disclose; N. Parashar, Nothing to Disclose; G. Horga, Nothing to Disclose.

T86. Brain Arachidonic Acid Metabolism Is Upregulated in Rat Model of Human HIV-1 Infection and Can Be Dampened by Chronic Lithium: Relation to Bipolar Disorder

Stanley I. Rapoport*, Mireille Basselin, Ipolia Ramadan

National Institute on Aging, NIH, Bethesda, Maryland

Background: With the introduction of Highly Active Antiretroviral Therapy (HAART), life expectancy has been markedly prolonged in HIV-1 infected patients, but so has prevalence of neuropsychiatric and HIV associated neurocognitive dysfunction (HAND). Bipolar disorder (BD) and substance abuse are risk factors for HIV-1 infection, and seropositive HIV-1 patients with BD are less drug-compliant and more prone to engage in unprotected sex. Neuroinflammation associated with upregulated arachidonic metabolism has been reported in postmortem brain from each disorder. Using neuroimaging, we reported that chronic lithium downregulated brain arachidonic acid (AA) metabolism in control rats and a rat lipopolysaccharide model of neuroinflammation. *Hypothesis*. Ten-mo old non-infectious HIV-1 transgenic (Tg) rats, which demonstrate neuroinflammation and behavioral changes, will show brain upregulated AA metabolism. Upregulation can be dampened by chronic lithium treatment.
Methods: Regional brain AA incorporation coefficients k* (radioactivity normalized to integrated plasma radioactivity) and rates J_{in} (k* times plasma unesterified AA concentration), markers of brain AA metabolism, were measured in 81 brain regions using quantitative autoradiography, after 5-min intravenous [1-^{14}C]AA infusion, in unanesthetized 10-month-old HIV-1 Tg and wildtype rats that had been fed a control or LiCl diet for 6 weeks.
Results: Regional k* and J_{in} for AA were significantly higher in HIV-1 Tg than wildtype rats fed the control diet. Lithium feeding, to produce a therapeutically relevant concentration (0.7 mM), reduced plasma unesterified AA concentration in both groups, and dampened the increments in k* (19 of 54 regions) and J_{in} (77 of 81) in the HIV-1 Tg rats.
Conclusions: Brain AA metabolism is upregulated in 10-mo old HIV-1 Tg compared to wildtype rats, consistent with neuroinflammation, and upregulated metabolism can be dampened by lithium treatment. Extrapolating, treatment with lithium or other mood stabilizers that downregulate rat brain AA metabolism (carbamazepine, valproate, lamotrigine) may improve cognition and reduce BD symptoms in HIV-1 patients with HAND through a comparable dampening effect on AA metabolism. A controlled clinical trial with lithium is ongoing in HIV-1 patients. Brain changes in such trials might be followed using positron emission tomography (PET) and ^{11}C- or ^{18}F-AA.
Keywords: Lithium, arachidonic acid, HIV, bipolar disorder, neuroinflammation
Disclosure: S. Rapoport; M. Basselin; I. Ramadan

T87. Gray Matter Volumes in Pediatric Generalized Anxiety Disorder: a Voxel-based Morphometry Study

Jeffrey Robert. Strawn*, Anna M. Wehry, Michael Cerullo, James Eliassen, Stephen Strakowski, Caleb Adler, Melissa DelBello

University of Cincinnati, Cincinnati, Ohio

Background: Anxiety disorders are common in children and adolescents, are associated with an increased risk of suicidality, and increase the likelihood of other psychiatric conditions. Generalized anxiety disorder (GAD) is among the most prevalent psychiatric illness affecting adolescents; however, despite its prevalence and associated morbidity, only recently has the neuroanatomy of GAD been systematically evaluated. To date, most neuroimaging studies of GAD in adolescents have used fMRI and have implicated abnormalities in structures that modulate emotional expression and fear processing, such as amygdala and ventrolateral prefrontal cortex. Nonetheless, there are few structural evaluations of the neurocircuitry of GAD in adolescents. Understanding neurostructural abnormalities associated with GAD in adolescence might identify potential pathophysiologic mechanisms by which response to treatment interventions could be assessed, potentially leading to biomarkers of treatment response. With these considerations in mind, we compared gray and white matter volumes between adolescents diagnosed with GAD and healthy subjects using voxel-based morphometry. We hypothesized that decreased gray matter volumes would be observed in cortical structures that have been previously implicated in anxious attachment, a fundamental aspect of pediatric anxiety disorders.
Methods: Structural MRI scans were obtained, at 4.0 Tesla, from 15 adolescents with GAD and 28 healthy adolescents. Image processing was performed using statistical parametrical mapping software (SPM8, Wellcome Department of Cognitive Neurology, University College London, UK). Images were segmented in native space and gray matter partitions were then normalized to the corresponding SPM8 tissue-probability map. The normalization parameters from this transformation were applied to the original

images, yielding a normalized whole brain image. These images were segmented and again, modulated with a newly extracted, individual brain mask and then resampled in 1 x 1 x 1mm resolution. To permit detection of true gray matter volume changes, images were modulated by the Jacobian determinant of the normalization matrix, resulting in images that take into account global and local volume changes during spatial normalization. Findings were defined as statistically significant at a level of $p < 0.001$ with a minimum cluster size of 200 voxels.

Results: There were no significant differences in race, age, or sex among the two groups. Healthy subjects had greater gray matter volumes in the right pre-central gyrus and right precuneus compared to adolescents with GAD. Additionally, gray matter volumes were decreased in the left orbital gyrus and right posterior cingulate in GAD. Finally, patients with GAD had greater white matter volumes in the left inferior temporal gyrus. By contrast decreased white matter volumes were observed in the left medial and superior frontal gyri in GAD.

Conclusions: Consistent with our initial hypothesis, we observed alterations in gray matter volumes in the right precuneus, right posterior cingulate and the left orbitofrontal cortex in GAD. The notion that structures that subserve attachment are neuroanatomically altered in youth with GAD is of potential clinical significance since attachment-based interventions may serve as a basis for effective psychotherapies for anxiety. It is noteworthy that, in prior investigations of adolescents with GAD, the precuneus and posterior cingulate exhibit decreased connectivity with the amygdala, structures which are functionally hyperresponsive to fear-related stimuli in adolescents with GAD. Thus, the present findings raise the possibility that these differences in connectivity may be associated with primary structural changes rather than being secondary to changes elsewhere in a larger affective network. Additionally, we observed decreased gray matter volumes in the left orbitofrontal gyrus in adolescents with GAD. This structure is intimately connected with the amygdala and functional abnormalities in this region have been reported in emotional processing and regulation of anxiety-associated physiological responses in adults with anxiety disorders. Moreover, there is decreased connectivity between this region and amygdala in adults with anxiety disorders. In lower primates, orbitofrontal cortex lesions accentuate conditioned fear responses. These previous reports suggest that deficits in fear regulation by the orbitofrontal cortex, and the associated anxiety, may be related to decreased gray matter volumes within this structure in adolescents with GAD.

Keywords: generalized anxiety disorder; pediatric; VBM

Disclosure: J. Strawn, **Part 4:** Dr. Strawn receives research support from Eli Lilly and Shire as well as from the American Academy of Child & Adolescent Psychiatry; A. Wehry, Nothing to Disclose; M. Cerullo, **Part 4:** Dr. Cerullo receives research support from the National Institues of Mental Health; J. Eliassen, Nothing to Disclose; S. Strakowski, **Part 3:** Eli Lilly, Janssen/J&J, AstraZeneca, Sumatomo, Pfizer, NIDA, NIAAA, NIMH, NARSAD (details available with the University/UC Physicians); C. Adler, **Part 3:** Merck, **Part 4:** AstraZeneca; Eli Lilly and Company; Pfizer; Otsuka; Forest; Sunovion; Novartis; Glaxo Smith-Kline; Amylin; M. DelBello, Nothing to Disclose.

T88. An Examination of White Matter Aberrations in Youth at High-risk for Bipolar Disorder: A Tract-based Spatial Statistics Analysis

Donna Roybal*, Naama Barnea-Goraly, Ryan G. Kelley, Spencer Boucher, Meghan Howe, Dylan Alegria, Kiki Chang

Stanford University, Palo Alto, California

Background: Previous neuroimaging studies suggest white matter (WM) structural differences between youth with bipolar disorder (BD), youth at high-risk (HR) for BD, and healthy controls (HC)[1]. To examine whether these abnormalities predate the onset of mania, we examined WM structure in youth at HR for BD, before their first putative manic episode, using diffusion tensor imaging.

Methods: ***Participants*** We scanned 24 children at HR for BD from 9-19 years old and 16 gender and age matched HC that were recruited from the community. The HR group was defined as having at least one biological parent with BD I or BD II as defined by Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and having attention-deficit/hyperactivity disorder with moderate mood symptoms or a history of a major depressive episode. HC had no current or lifetime psychiatric disorder, nor had any first-degree relative with any DSM-IV psychiatric diagnosis. Children were allowed to continue medications, except for stimulants, which were discontinued 24 hours prior due to another study involving a functional magnetic resonance (MR) imaging scan. ***Image acquisition and analysis*** MR images were acquired using a GE-Signa 3-Tesla scanner using a DTI sequence with 64 slices in 60 diffusion directions. DTIstudio (https://www.mristudio.org) was used to inspect image quality and to create a Fractional Anisotropy (FA) image, based on calculated FA for each voxel. Whole brain voxelwise analyses were then performed in FSL (v4.1.9) using Tract-based Spatial Statistics (TBSS v1.2). General Linear Models were created in FSL to investigate differences between the HR group and controls. Statistical analysis of the data was then submitted to voxelwise regression statistics using Threshold-Free Cluster Enhancement and permutation analysis implemented in FSL ("randomise"). All statistical analyses were fully corrected using Family-Wise Error.

Results: Results show a main effect of group, with HR demonstrating significantly increased FA ($p < 0.05$, corrected) in the uncinate fasciculus, fornix, body of the corpus callosum (CC), anterior thalamic radiations (ATR) bilaterally, subgenual and mid-cingulate gyrus, inferior fronto-occipital fasciculi bilaterally, internal and external capsules, and the superior and inferior longitudinal fasciculi bilaterally.

Conclusions: Youth at HR for BD showed increased FA in WM tracts connecting areas of the brain responsible for mood regulation, motor activity, executive functioning, and attention processing. These areas reflect the symptomatology seen in BD. We previously published data on WM aberrations in youth with BD when compared to HC and found decreased FA in the CC, ATR, and fornix using TBSS.[2] Therefore, prior to a manic episode, the HR group appears to have increased FA, while after a manic episode, youth with BD have decreased FA in similar regions. This developmental difference suggests a profound effect of mania on the developing brain. At a cellular level, increased FA in youth at HR for BD may suggest increased myelination and therefore connectivity in these areas, reflective of prodromal symptomatology. It could also suggest decreased axonal diameter or decreased density.[3] Other factors not related to myelin have also been implicated as mediators for increased FA, specifically decreased fiber crossing or fewer neuronal branchings[3]. Previous studies in disorders with known cognitive deficits have found associations between worsening cognitive deficits and increased FA in possible compensatory pathways.[4,5] However, as patients with BD commonly have cognitive deficits,[6] it may be that those at risk for BD have WM aberrations that are reflective of both compensatory processes to these deficits as well as increased connectivity reflected in prodromal symptomatology. These pathways then erode after repeated mood episodes. Disrupted WM architecture may then lead to functional disturbances in network connectivity and further mood dysregulation.

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Keywords: Diffusion tensor imaging, Bipolar, Adolescents, TBSS, White matter
Disclosure: D. Roybal, **Part 4:** American Academy of Child and Adolescent Psychiatry/ Lilly Pilot Research Award, 2012-2013, American Psychiatric Institute for Research and Education (APIRE)/ Janssen Resident Psychiatric Research Scholar, 2010-2011; N. Barnea-Goraly, Nothing to Disclose; R. Kelley, Nothing to Disclose; S. Boucher, Nothing to Disclose; M. Howe, Nothing to Disclose; D. Alegria, Nothing to Disclose; K. Chang, **Part 4:** Research support from GlaxoSmithKline and Merck.

T89. The Use of MRI to Detect Regionally Specific Changes in White Matter Integrity Following Extended Methamphetamine Self-administration in Rats

Carmela M. Reichel, Saeid Taheri, Ronald E. See*

Medical University of South Carolina, Charleston, South Carolina

Background: Methamphetamine (meth) is one of the most prevalent drugs of abuse worldwide. Meth poses unique challenges for treatment due to the highly addictive nature of the drug and multiple associated symptoms. A recent diffusion tensor imaging (DTI) study comparing human meth addicts to healthy controls suggested axonal injury and loss of myelination in both cortical and subcortical brain regions. However, studies in humans are limited by the inability to control for the premorbid state, the degree of meth use over time, and the extent of withdrawal. With the advent of new techniques for *in vivo* brain imaging in rats, we have begun to systematically map the progression of meth-induced degradation over time. Here, we report on white matter integrity following extended meth self-administration using DTI to assess the organization or integrity of white matter fiber bundles.
Methods: Male Long-Evans rats experienced daily sessions (6 hr/day for 2 weeks) of lever pressing for intravenous meth (0.02 mg/infusion) paired with the presentation of stimulus cues (light + tone). Rats underwent 4 *in vivo* imaging sessions. Imaging occurred before self-administration (Scan 1), 24 hrs after meth (Scan 2), abstinence day 7 (Scan 3), and abstinence day 28 (Scan 4). Anatomical and diffusion imaging were performed on a 7T BioSpec dedicated research MR scanner under isoflurane gas (1.5-2.0%) with a volume coil as the RF transmitter and a four channel surface array coil as the RF receiver. For diffusion measurements, we used DTI with the following parameters: TE/TR 23/5000 ms, diffusion directions 30, b 100, 850, and 1850 s/mm2, FOV 4.0 cm x 4.0 cm, slice thickness 1 mm interlaced, slice gap 0.1 mm, number of slices 12, matrix 128 x 128, number of averages 4, receiver bandwidth 250 kHz. This parameter selection resulted in spatial coverage of 19.2 cm and a special resolution of 312 μm. Raw diffusion images were processed with software developed in house to generate diffusion parameter maps. Mean values of diffusion parameters were calculated in regions of interest, which were manually drawn after post processing the parametric maps.
Results: Rats escalated meth intake over the long access period. Extended access to self-administered meth caused regionally specific changes in white matter integrity. Specifically, in the corpus callosum, fractional anisotropy (FA) values increased over the four weeks of meth abstinence indicating a loss of white matter integrity (e.g., myelin damage). In the striatum, elevated FA values were present on the first day of abstinence, but these values returned to control levels by the fourth week indicating some degree of recovery in striatal areas.
Conclusions: These novel imaging data incorporated a longitudinal assessment of meth-induced microstructual changes over time. Our findings suggest regional variations in altered white matter, such that recovery may occur in one region, while other fiber tracts are more susceptible to adverse long-term consequences. The lasting damage in callosal fibers produced by chronic meth suggests that behavioral deficits seen in meth addicts may be related to reduced interhemispheric communication.
Keywords: methamphetamine, self-administration, diffusion tensor imaging, escalation, abstinence, relapse
Disclosure: C. Reichel, Nothing to Disclose; S. Taheri, Nothing to Disclose; R. See, Nothing to Disclose.

T90. Functional Activation Differences during an Impulsivity Task Occur in Subjects with Bipolar Disorder Compared to Major Depressive Disorder during a Depressive Episode

Michael Cerullo*, Martine Lamy, Christopher Smith, Brenda Milburn, David E. Fleck, James Eliassen, Jeffrey Strawn, Caleb Adler, Melissa DelBello, Stephen Strakowski

University of Cincinnati, Cincinnati, Ohio

Background: Bipolar disorder (BPD) is a serious psychiatric illness that affects approximately 1.5% of the U.S. population and represents a significant source of individual morbidity and societal cost. Patients with BPD spend considerably more time with depressive rather than manic symptoms and suffer greater morbidity during periods of depression. However, little research has focused on the neurophysiology of depression associated with BPD. Major depressive disorder (MDD) and BPD have different treatments and illness courses and there is preliminary evidence that patients with these disorders exhibit different alterations in the cortico-limbic networks responsible for emotional homeostasis. Differences in neuronal activation between MDD and BPD patients during a depressive episode may point more directly to the etiology of depression in each disorder. Impulsive behavior is a core feature of BPD but not MDD. Therefore measuring impulsivity on a naturalistic reward processing task during fMRI may show differences in reward-related networks in each disorder. We hypothesized that BPD patients would show hyperactivation in limbic and reward regions compared to patients with MDD.
Methods: Twenty-one patients with BPD and 22 patients with MDD were recruited from the Cincinnati community. Following informed consent, all subjects were evaluated using the Structured Clinical Interview for DSM-IV and both patient groups were unmedicated and recruited during a depressive episode. All subjects were scanned at the University of Cincinnati College of Medicine's Center for Imaging Research (CIR) using a 4.0 Tesla Varian Unity INOVA Whole Body MRI/MRS system (Varian Inc., Palo Alto, CA). During the fMRI task, subjects performed the Balloon Analogue Risk Task (BART). During the BART task subjects score points by pumping up a series of balloons on the screen. After an unpredictable number of pumps, the balloon may pop, which results in a loss of all the points accumulated in the counter (but not the bank). The risk of explosion and points loss increases as a balloon expands, and points accumulates in the counter. Participants are considered more impulsive if they commit more pumps before banking (at the risk of losing their accumulated winnings on the trial). An event related design was used to model the experiment, and absolute times for each event (Pump, Pop, and Cash Out times) were used in the deconvolution algorithm to obtain a measure of activation in the final analysis.
Results: There were no statistically significant differences in race, age, education, gender, or YMRS scores between the two patient groups. Patients in the MDD group had significantly higher HAM-D scores ($F(1,21) = 7.5$, $p < .01$). The patient groups performed similarly on the BART task and there were no statistically significant differences in the adjusted BART score (i.e. the average number of pumps a subject committed before cashing out). Compared to patients with MDD, BPD patients exhibited increased activation in the cerebellar vermis, left lingual gyrus, and right middle frontal gyrus during cash out events. During pop events, BPD subjects exhibited increased activation in the

left inferior frontal gyrus, left lingual gyrus, and left fusiform gyrus. All brain activation differences reported were significant at $p < 0.01$ with a cluster correction of 20 contiguous voxels.

Conclusions: Compared to patients with MDD, BPD patients showed increased activation in reward processing regions (i.e. middle and inferior frontal gyrus) as well as in posterior perceptual regions (i.e. lingual and fusiform gyrus) and the cerebellar vermis. The different activation in the frontal regions supports our original hypothesis of altered reward processing in BPD compared to MDD. Prior fMRI studies have found activation differences in BPD compared to healthy subjects in the vermis and posterior perceptual regions. Accordingly the vermis has been shown to be involved in emotional regulation and therefore could play a role in impulsivity via the interaction of reward and limbic regions. Differences in visual processing regions suggest perceptual changes in BPD. Overall, the current findings support our general premise that MDD and BPD may be caused by different underlying neurophysiological mechanisms, and that these alterations in brain networks related to reward processing and emotion may provide targets for future therapeutic interventions.

Keywords: Bipolar Disorder, fMRI, Impulsivity, mood disorders, cognitive neuroscience

Disclosure: M. Cerullo, Nothing to Disclose; M. Lamy, Nothing to Disclose; C. Smith, Nothing to Disclose; B. Milburn, Nothing to Disclose; D. Fleck, Nothing to Disclose; J. Eliassen, Nothing to Disclose; J. Strawn, Nothing to Disclose; C. Adler, **Part 1:** AstraZeneca, Eli Lilly, Pfizer, Otsuka, Forest, Sunovion, Novartis, Glaxo Smith-Kline, AmylinResearch Support (multi-site trials), AstraZeneca, Eli Lilly, Pfizer, Otsuka, Forest, Sunovion, Novartis, Glaxo Smith-Kline, Amylin, Research Support (direct research funding), AstraZeneca, Lecture Bureau, Merck, Consulting, Merck, **Part 4:** AstraZeneca, Eli Lilly, Pfizer, Otsuka, Forest, Sunovion, Novartis, Glaxo Smith-Kline, Amylin; M. DelBello, **Part 1:** Research Support, AstraZeneca, Eli Lilly, Johnson and Johnson, Janssen, Pfizer, Otsuka, Sumitomo, NIDA, NIMH, NIAAA, NARSAD, GlaxoSmithKline, Merck, Novartis, Lundbeck, Lecture Bureau, Bristol-Myers Squibb, Merck, Consulting/Advisory Board/ Honoraria, Merck, Schering-Plough, Pfizer, **Part 4:** Research Support, AstraZeneca, Eli Lilly, Johnson and Johnson, Janssen, Pfizer, Otsuka, Sumitomo, NIDA, NIMH, NIAAA, NARSAD, GlaxoSmithKline, Merck, Novartis, Lundbeck; S. Strakowski, **Part 1:** Recent Research Support (grants to UC or UCP Psychiatry): as PI – NIMH; as co-investigator - Eli Lilly, Janssen/J&J, AstraZeneca, Sumatomo, Pfizer, NIDA, NIAAA, NIMH, NARSAD (details available with the University/UC Physicians), Consultant: University of Nebraska, Consultant: University of Utah, Speaking: Johns Hopkins University, Other: Directed discussion on Web MD, **Part 4:** Recent Research Support (grants to UC or UCP Psychiatry): as PI – NIMH; as co-investigator - Eli Lilly, Janssen/J&J, AstraZeneca, Sumatomo, Pfizer, NIDA, NIAAA, NIMH, NARSAD (details available with the University/UC Physicians).

T91. Self-regulation of Amygdala Activity with Real-time fMRI Neurofeedback in Patients with Depression

Kymberly Young*, Raquel Phillips, Vadim Zotev, Wayne C. Drevets, Jerzy Bodurka

Laureate Institute for Brain Research, Tulsa, Oklahoma

Background: Up to two-thirds of patients with major depressive disorder (MDD) who seek standard pharmacological and/or psychological interventions will not respond, while only one-half who do will achieve sustained remission. Cognitive-behavioral therapy (CBT), the most commonly implemented psychological treatment for MDD, is most effective for mildly to moderately depressed patients. In severely ill patients, CBT is often ineffective, and treatments available for these severally ill non-responders (such as electroconvulsive therapy, vagus nerve stimulation, and deep brain stimulation) are invasive, expensive, and pose significant risks. Therefore, there is a need to develop novel and non-invasive treatments for MDD. MDD is associated with the deregulation of brain emotional circuitry, with significant changes in amygdala activity. Research has shown that the hemodynamic response of the amygdala is exaggerated to negative stimuli in MDD, with further evidence that amygdala responses to *positive* stimuli are *attenuated* in MDD, and that this later response normalizes with remission. The availability of real-time functional magnetic resonance imaging (rtfMRI) and recent advances in rtfMRI neurofeedback (rtfMRI-nf) permit, for the first time, direct targeting of this region. The current study aims to determine whether individuals with MDD are able to use rtfMRI-nf to enhance the hemodynamic response of the amygdala to positive stimuli, and whether this ability will correspond to alterations in mood.

Methods: Unmedicated participants with a current diagnosis of MDD participated in the current study ($n = 19$). Twelve received active rtfMRI-nf with the left amygdala (LA) as the target region of interest (ROI), and 7 received sham feedback in which the target ROI was the left horizontal segment of intraparietal sulcus (HIPS), a region putatively not involved in emotional regulation. In each of four 8 min runs, alternating 40 s blocks of Rest, Count, and Happy were presented. During Rest blocks participants were instructed to clear their minds and focus on the screen. During Count blocks participants were instructed to count backwards from 300 by the number provided. During Happy blocks, the cue "Happy" and two colored bars (red, blue) were displayed on the screen. The red bar represented the actual BOLD neurofeedback signal from the target ROI, which was updated every 2 s by changing the height of the bar. Subjects were instructed to retrieve and contemplate positive autobiographical memories while also attempting to increase the level of the red bar to that of the fixed target level displayed by the blue bar. The target blue bar level was increased from run to run. A final 8 min Transfer run was presented in which no feedback was provided. Additionally, an 8 min rest run was included at the beginning and end of the fMRI session. All imaging was conducted on a GE Discovery MR750 3T MRI scanner with an 8-channel receive-only brain coil. Single shot gradient-recalled EPI with sensitivity encoding (SENSE) was used for fMRI with FOV/slice = 240/ 2.9 mm, TR/TE = 2000/30 ms, SENSE = 2, 96×96 matrix, flip = 90°, 34 axial slices. A T1-weighted MPRAGE sequence was used for anatomical reference and to define ROIs. Neurofeedback was implemented using a custom real-time fMRI system utilizing AFNI real-time features and a custom GUI software. For each subject, three spherical ROIs (7 mm radius in Talairach space) were centered, respectively, at the left and right amygdala and the HIPS region. The fMRI data analysis was based on GLM and performed in AFNI.

Results: Four of the MDD patients in the active rtfMRI-nf group were unable to learn to successfully regulate their amygdala (defined as LA BOLD response no different from 0 during the transfer run) and were therefore excluded from the group analysis. These patients were significantly younger and had increased fatigue ratings compared to those patients in the active group who successfully regulated their LA. The remaining 8 participants in the active rtfMRI-nf group significantly increased their LA response (BOLD response for Happy-Rest condition > 0) and maintained this elevated activity during the transfer run in which no neurofeedback was provided ($p = 0.03$). In the sham neurofeedback group, the BOLD response within the LA did not significantly increase from 0 in any of the training or transfer runs ($ps > 0.10$). The difference between the active and sham groups in LA activity was significant for the last training run and the transfer run ($ps < 0.05$). BOLD activity did not significantly change within the right amygdala or HIPS for either the active or sham groups ($ps > 0.11$). State measures of happiness significantly increased, while state measures of depression significantly decreased in the group receiving active rtfMRI-nf ($ps < 0.05$), but did not change significantly in the group that received sham feedback ($ps > 0.15$).

Conclusions: Our results show that by using rtfMRI-nf from the LA during recall of positive autobiographical memories, a subset of individuals with MDD can learn to self-regulate their amygdala BOLD responses. We also found an association between the ability to regulate the LA and reductions in depression ratings, as well as improvements in happiness ratings. These preliminary results suggest applications for

rtfMRI-nf training and positive autobiographical memory recall in the treatment of MDD.
Keywords: Depression, amygdala, autobiographical memory, neurofeedback, fMRI
Disclosure: K. Young, Nothing to Disclose; R. Phillips, Nothing to Disclose; V. Zotev, Nothing to Disclose; W. Drevets, Nothing to Disclose; J. Bodurka, Nothing to Disclose.

T92. Assessment of Brain Kappa Opioid Receptor Occupancy after Single Oral Doses of LY2456302 as Measured by PET with the Radioligand LY2879788 in Healthy Subjects

Johannes Tauscher*, Francois Vandenhende, Jennifer Witcher, Mohini Ranganathan, Ming-Qiang Zheng, Mika Naganawa, Yiyun Huang, Alexander Neumeister, Richard E. Carson

Eli Lilly and Co., Indianapolis, Indiana

Background: LY2456302 is a novel high-affinity, selective antagonist for kappa opioid receptors (κ-OR), which is currently in clinical development for the treatment of neuropsychiatric disorders. It displayed at least a 30-fold functional selectivity over mu and delta OR as demonstrated by *in vivo* receptor occupancy (RO) and pharmacology. The κ-OR antagonist PET tracer LY2879788 ([^{11}C]PKAB) was developed in collaboration with the Yale PET Center: we demonstrated earlier that LY2879788 binds specifically and reversibly to human brain κ-OR; that κ-OR binding can be quantitatively analyzed using a multi-linear model over 90 minutes post injection, with arterial input function and metabolite correction leading to an acceptable test-retest reproducibility of <10% intra-subject variability in kappa-rich brain regions; and that LY2879788 has an acceptable radiation dosimetry allowing repeated injections.
Methods: This single-center, open-label, 5-cohort, single dose study assessed target engagement of brain kappa opioid receptors after single oral doses of LY2456302 as measured by positron emission tomography (PET) with the radioligand LY2879788. Kappa opioid distribution volumes were obtained using Ichise's multilinear analysis 1 (MA1), and RO values were calculated in kappa opioid receptor-rich regions of interest (ROI) based on the Lassen plot. For each postdose PET scan, RO values were summarized by and compared between doses with a 2-way analysis of variance (ANOVA). Additionally, we explored the relationship between LY2456302 dose, plasma concentrations, and kappa opioid RO. A total of 13 healthy subjects, all male, participated in this study. The mean age was 35.4 years (range: 22-49); most subjects were black (69.2%) and not of Hispanic or Latino ethnicity (92.3%). All subjects completed the study.
Results: Single oral doses of 0.5 to 25 mg LY2456302 penetrated the blood-brain barrier, led to specific target engagement, and blocked significantly and in a dose-related manner κ-OR in the brain. Approximately 2 hours postdose ("peak scan"), brain κ-OR were almost saturated at doses of 10 mg or more. Sustained and substantial target engagement was observed for at least 24-hours. RO appeared to decline in parallel with the LY2456302 plasma concentration, indicating a negligible time lag in equilibration with the CNS compartment. A sigmoidal E_{max} PK/RO model, which assumes a direct relationship between plasma concentration of LY2456302 and RO, was fit to the data. According to this model, the E_{max} of LY2456302 was 93% and the plasma EC_{50} was estimated at 0.6 ng/mL. Single oral doses of up to 25 mg LY2456302 were well tolerated; there were no serious Adverse Events (AEs). The majority of AEs were associated with study procedures, particularly site pain and hematoma from the intravenous catheter used for repeated blood sampling.
Conclusions: LY2456302, when administered as single, oral doses of 0.5 to 25 mg penetrated the blood-brain barrier and blocked significantly and in a dose-related manner, kappa opioid receptors in the brain. Approximately 2 hours post-dose, nearly complete saturation of kappa receptors was observed at doses of 10 mg or more. Substantial and sustained target engagement was observed for at least 24 hours post-dose. Given that a single oral dose of 10 mg LY2456302 almost completely saturated κ-OR at 2 hours post-dose ("peak" scan), and that the lower bound of the observed kappa opioid RO at 24 hours post-dose ("trough" scan) exceeded 60%, a dose of 10 mg LY2456302 appears most suited for further clinical testing.
Keywords: Positron Emission Tomography, Drug Development, Receptor Occupancy, Kappa Opoid Receptors
Disclosure: J. Tauscher, **Part 1:** Employee and Stockholder of Eli Lilly and Co. since 2004, **Part 2:** see above, **Part 3:** see above; F. Vandenhende, **Part 1:** Owner of Clinbay, a statistical CRO that provides statistics and modelling solutions to the healthcare industry; J. Witcher, **Part 1:** I am an Emplyee and Stockholder of Eli Lilly and Co., **Part 2:** see above, **Part 3:** see above; M. Ranganathan, **Part 4:** Dr. Ranganathan received research grant support administered through Yale University School of Medicine from Eli Lilly and Co.; M. Zheng, Nothing to Disclose; M. Naganawa, Nothing to Disclose; Y. Huang, **Part 1:** My spouse is an employee of Pfizer, Inc., **Part 4:** Research contract funding from Pfizer, Eli Lilly and Co., Abbott, BMS and GSK; Consultant for UCB Pharma; A. Neumeister, **Part 4:** I have received grant funding from Eli Lilly (H71-MC-MGDB); R. Carson, **Part 4:** Richard Carson has received scientific study funding from Eli Lilly, Pfizer, Abbott, BMS, Theravance, and Otsuka. Dr. Carson is a consultant for Eli Lilly.

T93. Association of Depression with Hippocampal Volume: Results from an Epidemiological Sample

E. Sherwood Brown*, Carroll W. Hughes, Roderick McColl, Ronald Peshock, A. John Rush, Julia Knypinski

UT Southwestern Medical Center, Dallas, Texas

Background: Numerous studies have reported smaller hippocampal volumes in people with major depressive disorder when compared to healthy controls. However, negative reports have also been published. The sample sizes of most of these studies were modest, and methods and participant characteristics differed between studies. In most of the studies, the race or ethnicity of participants was either not addressed or the samples were almost exclusively non-Hispanic White persons. In the current study, data were used from an epidemiological sample of Dallas, Texas to examine the relationship between current depressive symptoms and hippocampal volume in a racially and ethnically diverse population.
Methods: The Dallas HeartStudy (DHS) examines cardiovascular disease (CVD) risk factors in an epidemiological sample of 6,101 adult Dallas residents. The study intentionally oversampled for African Americans to explore CVD risk factors in this subpopulation. Although the primary aim of the study was related to CVD, participants were not selected based on the presence of CVD. As part of this study structural magnetic resonance images of the brain were obtained in 2,082 participants. After excluding participants with missing data on variables tested, 1,992 were included in this current analysis. Volumes of the hippocampus and other brain regions were quantified using FSL FIRST, an automated volumetric analysis program. Depressive symptoms were assessed with the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR), a 16-item, patient-rated instrument that assesses depressive symptom severity in the past seven days. Multiple linear regressions were conducted using hippocampal volume (right, left and total) as the dependent variable and QIDS-SR scores, age, gender, education, psychotropic medication use, total brain volume and race/ethnicity as independent variables.
Results: Participants were 58.3% women, 37.2% non-Hispanic White, 14.2% Hispanic, 46.6% African American, and 2.1% Other (e.g. Native American, Asian American). The mean age was 49.8 (± 10.5) years, and mean education level was 12.6 (± 2.7) years. A total of 10% were currently taking antidepressants. Mean QIDS-SR score was 5.1 (± 3.8). After controlling for demographic information and total brain volume, right, left and total hippocampal volumes were all inversely associated with total QIDS-SR score ($p < .05$). After adding race/ethnicity as an independent variable the significance of QIDS-SR scores was

attenuated. Similar findings were observed using a dichotomized QIDS-SR score of $\geqslant$ 16 (N = 46, consistent with severe or very severe depressive symptom severity) vs. $<$16 (N = 1,946) as a dependent variable. Adjusted hippocampal volumes were 7.0% smaller on the right, 7.7% smaller on the left and 7.3% total (left + right) in those with QIDS-SR scores $\geqslant$ 16 as compared to those with lower QIDS-SR scores. A subgroup analysis suggested that the strongest relationship between QIDS-SR scores and hippocampal volume was in non-Hispanic White persons, with weaker and/or less consistent relationships in African Americans, Hispanic persons and Other races.

Conclusions: This is, to our knowledge, the largest study to date that has examined the relationship between depression and hippocampal volume. Current depressive symptom severity was associated with smaller hippocampal volume. The findings support prior studies that have found smaller hippocampal volumes in depressed persons. However, the racial and ethnic differences observed suggest that the findings reported in prior studies may not be generalizable to persons who are not non-Hispanic White. Additional research on the relationship between depression and brain changes in diverse populations is warranted.

Keywords: Depression, Hippocampus, Ethnicity, Magnetic Resonance Imaging

Disclosure: E. Brown, **Part 4:** Research grant contracts with Sunovion Pharmaceuticals and AstraZeneca; C. Hughes, **Part 1:** Dr. Hughes serves as a consultant to BioBehavioral Diagnostics, Inc.; R. McColl, Nothing to Disclose; R. Peshock, Nothing to Disclose; A. Rush, **Part 1:** Dr. A. Rush has received consulting fees from Otsuka Pharmaceutical Co, Ltd, University of Michigan, and Brain Resource Ltd; speaker fees from Singapore College of Family Physicians; royalties from Guilford Publications and the University of Texas Southwestern Medical Center, and a travel grant from CINP, **Part 4:** Dr. A. Rush has received research support from the National Institute of Mental Health and Duke-NUS; J. Knypinski, Nothing to Disclose.

T94. Resting State Network Dynamics Predict Relapse in Cocaine-dependent Individuals

Meredith J. McHugh*, Hong Gu, Yihong Yang, Jacquelyn Braud, Michael D. Devous, Richard W. Briggs, N. Robrina Walker, Bryon Adinoff, Elliot A. Stein

Neuroimaging Reearch Branch NIDA-IRP, Baltimore, Maryland

Background: A major challenge in the treatment of cocaine addiction is identifying factors that predict recidivism. Relapse risk increases with the severity of symptoms experienced during abstinence from cocaine, including drug craving, emotional distress and cognitive deficits. It has been recently proposed that abstinence from drugs of abuse, such as cocaine, produce an alteration in resting connectivity within and between three large-scale cortical networks, the default mode network (DMN), executive control network (ECN) and the salience network (SN). Changes in network dynamics may be both driven by, and contribute to, the severity of symptoms experienced during cocaine abstinence. Consequently, resting state network dynamics may prove more sensitive to underlying abstinence-related processes than self-report or neurocognitive measures currently employed to assess symptom severity and relapse risk. The current study investigated whether resting state network dynamics measured at the end of a 2-4 week treatment episode could predict relapse to cocaine use.

Methods: 58 cocaine dependent individuals (52 males) and 23 healthy controls (15 males) completed 6-minute resting fMRI scans. Cocaine-dependent individuals completed scans immediately following 2-4 weeks of residential treatment (Minnesota Model). Within a week of this scan session, all individuals completed several neurocognitive and clinical measures, including the Trail Making Test, Wisconsin Card Sorting Test, Continuous Performance Task, Cocaine Craving Questionnaire and the Obsessive Compulsive Cocaine Use scale. Cocaine-dependent participants were followed for 168 days post-treatment with weekly urine analysis and clinical interview to assess for relapse. Resting fMRI data were preprocessed and analyzed using AFNI and FreeSurfer. Preprocessing involved slice-timing correction, motion correction, spatial normalization, nonlinear implicit reference-based group-wise image registration, spatial smoothing (FWHM = 6 mm) and quadratic polynomial detrending. Resting data were then submitted to a group-level independent component analysis to identify the DMN, ECN and SN. To assess within-network connectivity, individual component time-courses were generated then regressed against the entire brain using a dual-regression procedure. Cross-correlations between component time-courses were conducted to assess between network connectivity. Linear mixed effects models including gender as a covariate were conducted to assess group differences in within- and between-network connectivity.

Results: Individuals who relapsed within 30-days post-treatment ($n = 27$) exhibited enhanced connectivity within the DMN relative to healthy controls, with peak connectivity strength observed within the dorsal posterior cingulate cortex. In contrast, a pattern of enhanced connectivity between the left and right ECN was observed among individuals who had not relapsed by day 30 ($n = 31$) relative to both healthy controls and individuals who relapsed during this time. Mean connectivity within the right ECN, particularly the lateral parietal region, was in turn negatively associated with time to complete Trail B in the Trail Making Task, but only among individuals who relapsed by day 30. Together ECN and DMN connectivity correctly classified individual relapse status at day 30 in 74% of cases. A survival analysis demonstrated that connectivity between the left and right ECN predicted time to relapse up to 24 weeks months post-treatment. Importantly, clinical factors, such as cocaine craving, obsessive compulsive cocaine use, life-time use and use in the past 90 days were unrelated to relapse at day 30 or time to relapse over a 24 week period. Performance on neurocognitive measures was also unrelated to relapse risk.

Conclusions: Enhanced engagement of the ECN has been associated with a greater capacity to exert cognitive control as well as enhanced executive functioning and attention. In the current study, enhanced resting connectivity between the left and right ECN was associated with significantly reduced risk of relapse up to 5.5 months following short-term residential treatment. This occurred in the absence of significant relapse-related differences in neurocognitive measures assessing cognitive control, executive control and sustained attention. These findings suggest that resting ECN connectivity is more sensitive to processes that protect against relapse following short-term residential treatment for cocaine addiction than putative behavioral neurocognitive markers of ECN functioning. They also suggest that interventions that focus on enhancing resting connectivity within the ECN may improve treatment outcomes. In contrast, enhanced engagement of the DMN has been associated with drug craving, rumination and poor cognitive performance. The current study extends on this body of research by demonstrating that enhanced DMN resting connectivity predicts short-term relapse to cocaine use. Together, reduced ECN connectivity and enhanced DMN connectivity place individuals at the greatest risk of early relapse to cocaine use, risk that is not otherwise associated with clinical variables such as craving and cocaine use history. These findings highlight the potential utility of resting connectivity measures as a probe of treatment efficacy and relapse risk.

Keywords: cocaine addiction, resting connectivity, relapse, exectuive control, default mode

Disclosure: M. McHugh, Nothing to Disclose; H. Gu, Nothing to Disclose; Y. Yang, Nothing to Disclose; J. Braud, Nothing to Disclose; M. Devous, Nothing to Disclose; R. Briggs, Nothing to Disclose; N. Walker, Nothing to Disclose; B. Adinoff, Nothing to Disclose; E. Stein, Nothing to Disclose.

T95. Subcortical Food Motivation Circuitry Dysfunction Associated with Endogenous Active Ghrelin Levels in Women with Anorexia Nervosa

Laura M. Holsen*, Elizabeth A. Lawson, Kara Christensen, Anne A. Klibanski, Jill M. Goldstein

Harvard Medical School/Brigham and Women's Hospital, Boston, Massachusetts

Background: Anorexia nervosa (AN) is characterized by severe volitional weight loss, significant appetite-regulatory peptide abnormalities, and food reward circuitry brain dysfunction. Ghrelin, an orexigenic neuropeptide produced in the stomach, is elevated in women with chronic AN. Basal ghrelin levels normalize with recovery although secretory dynamics in response to food may not, suggesting a possible etiological role for this peptide. Further, we and others have demonstrated hypoactivation in regions associated with homeostatic and hedonic food motivation regions in response to food cues in women with chronic AN and women weight-recovered from AN. Despite evidence that ghrelin acts on subcortical brain regions shown to be disrupted in AN, such as the hypothalamus, amygdala, and hippocampus, there is a paucity of data focused on examination of these systems in parallel in women with AN. We present a study aimed at delineating the relationship between endogenous ghrelin levels and brain activity deficits in subcortical and cortical regions implicated in food motivation in women with AN and women weight-recovered from AN (AN-WR), compared with healthy control women with no history of AN.
Methods: Female participants [12 women with active, restricting-type AN, 9 women weight-recovered from restricting-type AN (AN-WR), 11 age-matched healthy control women (HC)] viewed high-calorie food, low-calorie food, and non-food (household objects) images while undergoing functional MRI (fMRI) scanning on a 3T Siemens Trio MR scanner before (*pre-meal*) and after (post-meal*) eating a 400 kcal meal. Peripheral active ghrelin levels were ascertained fasting and at 30, 60, and 120 minutes following standardized meal consumption. Data analysis*: fMRI data were analyzed using SPM8 to examine specific between-groups contrasts: High-calorie foods > objects; low-calorie foods > objects; AN vs. HC; AN-WR vs. HC; AN vs. AN-WR; separately in the pre- and post-meal states. Regions of interest (ROIs) included: hypothalamus (HYPO), nucleus accumbens (NAc), amygdala (AMYG), hippocampus (HIPP), insula (aINS), orbitofrontal cortex (OFC). Relationships between ROI activation (i.e., percent change in betas for group differences in brain activity comparing AN, AN-WR, HC) and active ghrelin levels (calculated as area under the curve; AUC) were examined using general linear models in SPSS.
Results: AN and AN-WR women had significantly higher active ghrelin levels (area under the curve; AUC) compared to HC women ($t = 2.46$ and 3.67, $p = 0.023$ and 0.002, respectively). Active ghrelin AUC was associated with a substantial proportion of *pre-meal* differences in activation between AN and HC in response to high-calorie foods in the left HYPO (17.5%) and left AMYG (14.3%), and post-meal* differences in activation between AN and HC in the left AMYG in response to high-calorie foods (18.3%) and low-calorie foods (10.5%). Further, active ghrelin AUC was associated with *pre-meal* differences in activation between AN-WR and HC in response to high-calorie foods in the right HYPO (53.0%), left HYPO (35.6%), and left AMYG (87.7%). Finally, in terms of activation differences between AN and AN-WR, active ghrelin AUC was associated with 15.0% of the variance in post-meal* group differences in the right HIPP in response to low-calorie foods. Active ghrelin AUC did NOT account for between-group variance in activation of cortical food motivation regions, including the aINS and OFC, or in subcortical regions without ghrelin receptors (NAc).
Conclusions: Results indicate associations between endogenous ghrelin secretion and brain activity deficits in women with chronic AN. Moreover, these relationships persist following weight recovery in women with a history of AN, suggesting they may be a trait characteristic of AN. Although preliminary, given the small sample size, findings can be considered robust given the consistency across contrasts (high- and low-calorie; pre- and post-meal), and restriction to subcortical regions in which ghrelin receptors have been identified (HYPO, HIPP) or to which dense direct ghrelinergic projections from the HYPO exist (AMYG). These data, the first to our knowledge to bring together separate lines of investigation into ghrelin and brain abnormalities in AN, serve as evidence for novel hormone-brain biomarkers to target in future interventional studies.
Keywords: fMRI, appetite, ghrelin, anorexia nervosa
Disclosure: L. Holsen, Nothing to Disclose; E. Lawson, Nothing to Disclose; K. Christensen, Nothing to Disclose; A. Klibanski, Nothing to Disclose; J. Goldstein, Nothing to Disclose.

T96. Resting-state Functional Connectivity and Neuroactive Steroids in Postpartum Depression

Kristina M. Deligiannidis*, Elif M. Sikoglu, Scott A. Shaffer, Blaise Frederick, Constance M. Moore, Anthony J. Rothschild

University of Massachusetts Medical School, Worcester, Massachusetts

Background: Postpartum depression (PPD) affects 1 in 8 women and negatively impacts infant attachment, cognitive development and behavior. Animal models suggest that differential regulation of neuroactive steroids during the perinatal period is associated with abnormal depressive-like maternal behavior through interaction with the γ-aminobutyric acid (GABA) system. Neuroactive steroids are allosteric modulators of $GABA_A$ receptor function and alter excitability of the central nervous system. This study tested the hypotheses: (1) PPD would be associated with attenuation of connectivity between the anterior cingulate cortex (ACC) and bilateral amygdalae (AMYG), hippocampi (HIPP) and dorsolateral prefrontal cortices (DLPFC) as compared to healthy postpartum subjects and (2) mean postpartum plasma concentration of allopregnanolone would be lower in the PPD cohort and correlated to the total Edinburgh Postnatal Depression Scale (EPDS) score.
Methods: Thirty-two subjects were prospectively evaluated between 26-30 and 34-36 weeks gestation, less than 36 hours of parturition and between 3-9 weeks postpartum through serial plasma neuroactive steroid measurements and mood and psychosocial assessments. A subgroup of 17 postpartum women comprised of healthy comparison (HCS) ($n = 9$, mean age: 30.67 ± 3.81) and medication-free subjects who developed unipolar PPD (PPD) ($n = 8$, mean age: 28.62 ± 5.93) were examined using resting-state functional Magnetic Resonance Imaging (fMRI). Resting-state functional connectivity (rs-fc) analysis with seeds placed in the ACC, and bilateral AMYG, HIPP and DLPFC was performed. Data were acquired on a 3.0 Tesla Philips Achieva whole-body MR system (Philips Healthcare, Best, the Netherlands). T1-weighted anatomical MRI was acquired for diagnostic and localization purposes and all subjects underwent the resting-state fMRI scan with eyes open. Resting-state scan images were obtained using an EPI sequence. Resting-state fMRI data analysis was carried out by using Data Processing Assistant for Resting-State fMRI (DPARSFA-http://www.restfmri.net), which works with SPM8 (Statistical Parameter Mapping– Welcome Department of Imaging Neuroscience, London, UK). Following the preprocessing steps to regress-out physiological and other sources of noise, individual and group functional connectivity analyses were performed. The two groups' resting-state functional connections with each seed were compared voxelwise using a 2-sample *t*-test. The resulting maps were subjected to cluster analysis. Neuroactive steroids were quantified by a novel liquid chromatography/mass spectrometry (LC-MS/MS) method; analyzed on a NanoAcquity UPLC coupled to a Quattro Premier XE (Waters) triple quadrupole mass spectrometer operating in the positive ion electrospray mode. The quantitation limit was 0.2 ng/mL for all analytes. Pearson Chi-Squared tests for categorical and Mann-Whitney U tests

for continuous variables were done to compare the differences in demographic, medical and psychiatric history, current diagnostic and psychosocial measures and mean neuroactive steroid concentration between PPD and HCS postpartum subjects. Differences in neuroactive steroid concentrations and ratios of progesterone metabolites were compared between cohorts.
Results: There were no significant differences between cohorts in age, right-handedness, delivery type, breastfeeding status or time since delivery relative to the day of MRI. Subjects who developed PPD had a history of major depression ($\chi^2 = 13.39$, $p < 0.001$), generalized anxiety ($\chi^2 = 5.89$, $p < 0.05$), and social phobia ($\chi^2 = 4.10$, $p < 0.05$), at rates higher than the HCS cohort. 25% of women who developed PPD had a history of prior PPD ($p = ns$). The HCS cohort had significantly stronger connectivity between the ACC and left DLPFC and bilateral AMYG; between bilateral AMYG and ACC and bilateral DLPFC; between the left DLPFC and right AMYG, right HIPP and right DLPFC than the PPD cohort ($p < 0.01$, T-value > 2.60, minimum of 5 voxels for each cluster, $df = 15$). The concentration of progesterone had a significant positive relationship to the number of days since delivery ($r = 0.74$, $p = 0.004$). Between groups, neuroactive steroid concentrations and steroid ratios did not differ during pregnancy or in the postpartum ($p > 0.05$). Although it did not reach significance, there was a positive relationship between the concentration of allopregnanolone during pregnancy and the postpartum EPDS total score ($r = 0.696$, $p = 0.083$) at the time of MRI. Postpartum concentrations of pregnanolone, allopregnanolone and pregnenolone were all lower in the PPD cohort compared to HCS but the difference did not reach significance. Neuroactive steroid/progesterone ratios at the time of postpartum MRI had a negative relationship with the number of days since delivery but there was no difference between-groups ($p > 0.05$).
Conclusions: The present investigation is the first to assess resting-state functional connectivity and quantify neuroactive steroid concentrations in healthy postpartum subjects and subjects who developed PPD within 9 weeks of delivery. Disruption in functional connectivity in corticolimbic areas may contribute to disturbances of mood during a time of falling neuroactive steroid concentrations.
Keywords: Postpartum depression; resting-state functional connectivity; neuroactive steroids
Disclosure: K. Deligiannidis, **Part 1:** Elsevier: Society of Biological Psychiatry Travel Award to attend the 2011 annual scientific conference; Grant support from Forest Research Institute, **Part 4:** Forest Research Institute (investigator-initiated grant), unrelated to research poster submitted to ACNP for presentation; E. Sikoglu, Nothing to Disclose; S. Shaffer, Nothing to Disclose; B. Frederick, Nothing to Disclose; C. Moore, Nothing to Disclose; A. Rothschild, **Part 1:** received grant support from Cyberonics, Takeda, and St. Jude Medical and has served as a consultant to Allergan, GlaxoSmithKline, Eli Lilly, Noven Pharmaceuticals, Pfizer, Shire Pharmaceuticals, and Sunovian, **Part 4:** grant support from Cyberonics, Takeda, and St. Jude Medical.

T97. Neural Mechanisms of Social Influence in Young Adult Drug Use

Jodi M. Gilman*, Sang Lee, John Kuster, Byoungwoo Kim, Myoung Joo Lee, Paul Wighton, Andre van dew Kouwe, Anne Blood, Hans C. Breiter

Massachusetts General Hospital, Charlestown, Massachusetts

Background: Decades of research have demonstrated the importance of social influence in the initiation and maintenance of drug use (Kandel, 1973, Ong, 1989, Khavari, 1993, Bahr et al., 2005). Peers play a pivotal role in introducing an individual to a drug, and most drug use occurs in social and recreational settings. A survey of over 5,000 adolescents found that non-users of alcohol and tobacco scored significantly higher than users in the ability to resist peer pressure (Andrade Palos et al., 2009). Though social influence is a pivotal factor in drug use, little is known about neural mechanisms underlying social influence.
Methods: To better understand the role of social influence in drug use, we ran a study using a novel social decision-making paradigm in non-dependent marijuana-using young adults (MJ) aged 18-25, and age and gender-matched controls (CON) while they underwent functional magnetic resonance imaging (fMRI) scans. In this paradigm, subjects made a perceptual judgment after finding out how fictitious 'peers' had made the same judgment. They could either make a judgment that matched their peers (congruent) or one that went against their peers (incongruent). We performed an event-related design that allowed us to temporally separate events such as seeing a cue, seeing 'peer' judgments, making a choice, and receiving feedback. Participants were scanned using a 3T Siemens Trio scanner. Whole-brain high-resolution coronal structural scans were collected using a T1- weighted magnetization-prepared rapid gradient echo pulse sequence, and functional scans were acquired using a T2*-sensitive echoplanar sequence that measures changes in BOLD contrast (TR, 2s; TE, 30 ms; flip angle, 90°; matrix, 64 x 64; in-plane matrix, 128; FOV, 24 cm; slice thickness, 5 mm).
Results: We found a significant interaction between group (MJ or CON) and task behavior (congruent vs incongruent judgments) ($F = 3.98$, $p = 0.013$). Post-hoc Bonferroni tests indicated there was a significant difference only within the MJ group in the number of congruent vs incongruent choices ($p = 0.017$), indicating that MJ were more likely to make a judgment consistent with the group than were CON. We found no differences in neural activation between MJ and CON during congruent trials. During incongruent trials, MJ had significantly greater deactivation than CON in the bilateral nucleus accumbens (NAc), a region associated with social learning (Berns et al., 2010) and reward processing (Breiter et al., 1997, 2001). MJ also showed greater activation than CON during incongruent trials in the anterior cingulate (ACC), a region involved in conflict-monitoring (Berns et al., 2010).
Conclusions: MJ may experience more anxiety than CON when going against group decisions, which may be reflected in stronger conflict-related signals in the NAc. These results are consistent with data from a study showing that the NAc deactivated when subjects deviated from group opinion (Klucharez et al., 2009), and that deactivation of the NAc predicted conformity in future trials. The authors hypothesized that conformity was similar to reinforcement learning, in which deviation from group norms would trigger a neural response that was similar to prediction error and signal a 'mistake,' or a need to change behavior to be more in line with group norms. Other investigators have reported that the NAc can show both positive and negative signal change, corresponding to positive and negative input stimuli (Aharon et al., 2001) including somatosensory pain (Becerra et al., 2001), suggesting that the NAc processes both rewarding and aversive inputs (Breiter & Gasic, 2004). The negative signal observed raises an alternative hypothesis that MJ subjects experience the deviation from group norms as an aversive event. In MJ, the negative BOLD signal in the NAc during incongruent trials may either be a contributing factor to, or a result of, drug use behavior, and may be a possible biomarker in the development of addiction. A greater understanding of the neural mechanisms of peer influence may lead to the ability to predict who may be at highest risk for drug use in social situations, and allow clinicians to develop interventions to mitigate this risk.
Keywords: social influence, drug use, cannabis, imaging, adolescents
Disclosure: J. Gilman, Nothing to Disclose; S. Lee, Nothing to Disclose; J. Kuster, Nothing to Disclose; B. Kim, Nothing to Disclose; M. Lee, Nothing to Disclose; P. Wighton, Nothing to Disclose; A. van dew Kouwe, Nothing to Disclose; A. Blood, Nothing to Disclose; H. Breiter, Nothing to Disclose.

T98. Damage Control: The Neural Basis of Reappraisal in Generalized Anxiety Disorder

Carmen Andreescu*, Lei K. Sheu, Dana L. Tudorascu, Greg Siegle, Douglas Mennin, Howard J. Aizenstein

University of Pittsburgh, Pittsburgh, Pennsylvania

Background: Generalized anxiety disorder (GAD), defined by excessive and uncontrollable worry, has been associated with

deficits in emotion regulation through failure to engage the anterior cingulate cortex (ACC), exaggerated amygdala reactivity to warning cues preceding aversive/neutral pictures, disrupted connectivity patterns of the amygdala subregions. Among emotion regulation strategies, reappraisal is one of the best-studied cognitive strategies. In this study we explore the neural substrates of reappraisal in midlife and late-life GAD.

Methods: The data were collected from two studies conducted at the University of Pittsburgh. The fMRI block design involved an initial 5-min resting state phase followed by five blocks of the worry modulation task (five worry induction statements alternating with instructions to either suppress or reappraise worry). The data was collected on a Siemens Trio 3T scanner, using the pseudo-continuous Arterial Spin Labeling (pCASL) sequence. 24 slices were acquired using a gradient-echo EPI sequence. Imaging parameters: matrix size 64X64, TR/TE = 4000/25 msec, slice thickness 5 mm, gap = 1 mm. Functional MRI data were preprocessed using SPM 8. The PCASL data was analyzed using the SPM8 toolkit provided by Wang et al. BOLD signal was extracted from the PCASL data and used in the first level analysis. Behavioral data were collected in scan after each task block and was analyzed using a 2-way ANOVA (GAD/Controls, Suppression/Re-appraisal). Group analysis for fMRI data used SPM8 for the regression analysis (with worry ratings as covariate). ROI signals were extracted using REX (http://www.nitrc.org/projects/rex/). Results were normalized and plotted in Matlab 2010b. Functional connectivity was analyzed using the Conn Toolkit. We used the left DLPFC as seed to explore the functional connectivity in the Executive network. Connectivity maps for anxious and control subjects were compared using a bivariate correlation.

Results: Behavioral data*. Compared with non-anxious participants, GAD subjects have significantly higher worry ratings after reappraisal ($t = 2.23$, $p = 0.03$), but not after suppression ($t = 0.81$, p ns). Group Analysis*. When comparing the neural activation patterns between worry reappraisal and worry induction, GAD have greater activation in the left anterior insula than controls [$t = 3.07$, $p = 0.002$ (uncor), FWE-ROI corrected $p = 0.07$, x,y,z:-30,26,-8] (Fig 2). Time series analysis confirms the greater activation of left Anterior Insula during worry reappraisal in anxious subjects (Fig 3, left panel). Moreover, the time series analysis of the left_vlPFC shows a lower peak activation in GAD compared with controls (Fig 3, right panel). Regression Analysis*. Higher worry ratings during reappraisal (higher anxiety during reappraisal) in all subjects was associated with greater activation in the pregenual cingulate [$t = 3.24$, $p = 0.001$ (uncorr), $k_E = 44$, x,y,z = −0.68,37.7,-0.30]. Functional connectivity in the executive control network*. Compared with non-anxious participants, GAD have greater connectivity during reappraisal between the left dlPFC seed and subgenual cingulate (x,y,z = −0.68,11.25,-8.8), bed nucleus of stria terminalis (BNST) (x,y,z = 6.7, 6.4,-1), R parahippocampal cortex (x,y,z = 20.3,8.5,-30) and dorsal ACC (BA 24) (x,y,z = 8,8,41) [$t = 2.22$, $p = 0.005$ uncorr].

Conclusions: Anxious participants appear to have difficulties to effectively use reappraisal. This is congruent with various reports regarding the limited benefit of cognitive-behavioral therapy in GAD. The results showing greater lateral PFC activation during worry reappraisal in controls and greater left anterior insula activation in anxious participants suggests a neural model of a regulatory deficit and insular hyperactivity. The correlation of greater ACC activation in participants with higher worry ratings after reappraisal suggests that these participants have greater 'cognitive conflict' during reappraisal. Thus, normative cognitive reappraising strategies may be at odds with the engrained, compensatory strategies used during worry. These results are in concordance with the emotion dysregulation theory of pathologic worry. This model is further supported by the functional connectivity results. During reappraisal, GAD subjects have greater correlation indices between the left dlPFC seed and dACC and paralimbic structures, compared with non-anxious controls. This pattern of functional connectivity in the executive control network suggests both an attempt to manage a perceived conflict (e.g ambivalence regarding the appropriate regulation strategy) and an attempt to "control damage" (by controlling paralimbic structures involved in sustained threat and autonomic modulation).

Keywords: generalized anxiety, reappraisal, functional connectivity

Disclosure: C. Andreescu, Nothing to Disclose; L. Sheu, Nothing to Disclose; D. Tudorascu, Nothing to Disclose; G. Siegle, Nothing to Disclose; D. Mennin, Nothing to Disclose; H. Aizenstein, Nothing to Disclose.

T99. Diffusional Kurtosis Imaging of Frontal White Matter in Alcohol-dependent Young Adults with and without Attention Deficit Hyperactivity Disorder

Joseph P. Schacht*, Ali Tabesh, Konstantin E. Voronin, Raymond F. Anton

Medical University of South Carolina, Charleston, South Carolina

Background: Alcohol dependence is highly comorbid with attention deficit hyperactivity disorder (ADHD) (van Emmerik-van Oortmerssen et al., 2012), and dually diagnosed individuals drink more and experience greater impairment (Huntley & Young, 2012). In the brain, both disorders are independently associated with abnormal white matter microstructure, particularly along frontal tracts that connect subcortical areas with prefrontal regions that underlie cognitive control (Pfefferbaum et al., 2009; van Ewjik et al., 2012). However, there is little extant research on white matter integrity among dually diagnosed individuals. In this pilot study, we used a new diffusion imaging method, diffusional kurtosis imaging (DKI), which provides advanced measures of white matter microstructure, to quantify differences between alcohol-dependent young adults with and without ADHD. Unlike diffusion tensor imaging (DTI), DKI can measure non-Gaussian water diffusion. The degree of non-Gaussianity is quantified via the kurtosisof the diffusion distribution. Diffusional kurtosis conveys information about microstructural complexity that is complementary to conventional DTI metrics such as fractional anisotropy, perhaps reflecting the degree of myelination, packing density of axonal and fiber bundles, or axonal membrane permeability (Fieremans et al., 2011). Recent data suggest that kurtosis abnormalities are a more sensitive index of ADHD diagnosis than DTI metrics (Helpern et al., 2011).

Methods: Participants were 17 alcohol-dependent young adults (15 men, 2 women; mean age = 26.4 [SD = 4.0]), 8 of whom were classified as having ADHD by either the ADHD module of the Mini International Neuropsychiatric Interview or a score $\geqslant 9$ on the World Health Organization ADHD Self-Report Scale. Using a 3T Siemens TIM Trio scanner, diffusion-weighted images were acquired along 30 directions at each of two b-values (1000 and 2000 s/mm^2). Kurtosis measures were calculated on a voxelwise basis with Diffusional Kurtosis Estimator (Tabesh et al., 2011), and the resulting images were registered to a common white matter skeleton using tract-based spatial statistics (Smith et al., 2006). Mean kurtosis (MK) values were then extracted from 8 frontally distributed regions of interest (ROIs) defined by the Johns Hopkins University white matter tractography atlas: the left and right anterior internal capsule (AIC), external capsule (EC), and anterior corona radiata, and the body and genu of the corpus callosum. MK in each ROI was compared between participants with and without ADHD using the general liner model, controlling for age, gender, and ethnicity.

Results: Relative to those without ADHD, alcohol-dependent participants with ADHD had significantly lower MK in the left AIC ($F(1, 12) = 7.02$, $p \leqslant .05$), right EC ($F(1, 12) = 7.23$, $p \leqslant .05$), and body of the callosum ($F(1, 12) = 4.69$, $p \leqslant .05$). Group differences in the right AIC ($F(1, 12) = 3.98$, $p = .07$) and left EC ($F(1, 12) = 3.54$, $p = .08$) were in the same direction and approached significance.

Conclusions: These preliminary data suggest that young adults with comorbid alcohol dependence and ADHD may exhibit greater degradation of frontal white matter microstructure than those with alcohol dependence alone. The differences between groups in MK

of the AIC are of particular interest, as this tract includes fibers that connect the ventral striatum and prefrontal cortex, regions long implicated in both addiction and externalizing disorders. Microstructural differences in such tracts may be related to the poorer clinical course of dually diagnosed individuals, and could ultimately be used to identify individuals at greater risk for relapse. Comparisons of frontal MK between alcohol-dependent individuals with and without ADHD and healthy control participants are ongoing.

Keywords: Alcoholism, ADHD, neuroimaging, diffusion-weighted imaging, white matter

Disclosure: J. Schacht, Nothing to Disclose; A. Tabesh, Nothing to Disclose; K. Voronin, Nothing to Disclose; R. Anton, **Part 1:** Dr. Anton reports for the last three years, being a consultant or on the scientific advisory board for Eli Lilly, Glaxo Smith Kline, Alkermes, Lundbeck and Roche. Additionally, he has received support from Eli Lilly, Schering Plough, Lundbeck, Alkermes, GlaxoSmithKline, Johnson & Johnson, and Abbott Laboratories as part of the Alcohol Clinical Trials workgroup (ACTIVE). He also has received research contracts/grants from Lilly and Merck. He is a stockholder in Alcomed which has received STTR support from NIDA, **Part 4:** Dr. Anton has received support from Eli Lilly, Schering Plough, Lundbeck, Alkermes, GlaxoSmithKline, Johnson & Johnson, and Abbott Laboratories as part of the Alcohol Clinical Trials workgroup (ACTIVE). He also has received research contracts/grants from Lilly and Merck.

T100. APOE Genotype Modulates 1H-MRS Metabolites in the Aging Brain

Jesus J. Gomar*, Marc L. Gordon, Peter B. Kingsley, Aziz M. Ulug, Koppel Jeremy, Concepcion Conejero-Goldberg, Peter Davies, Terry E. Goldberg

North Shore LIJ, Manhasset, New York

Background: The use of proton magnetic resonance spectroscopy (^{1}H-MRS) has become a useful technique to quantify the concentration of cerebral metabolites of the brain *in vivo*. Alzheimer's disease (AD) patients show evidence of reduction of N-acetylaspartate (NAA)/Creatine (Cr) ratio and increase of choline (Cho)/Cr and myoinositol (mI)/Cr ratios. Mild Cognitive Impairment (MCI) patients tend to show similar ^{1}H-MRS metabolite pattern. ^{1}H-MRS studies on healthy aging have reported inconsistent findings, and only one small study investigated the role of APOE in the findings. Therefore, we sought to determine relations between APOE, age, and ^{1}H-MRS metabolite ratios. Additionally we examined these measures in relation to cognition by means of Structural Equation Modeling (SEM), a pathway-based statistical technique. We predicted that APOE and/or its interaction with age would impact cognition when mediated by MRS measures.

Methods: 112 subjects between 50 and 86 years were recruited. They had MMSE scores $>=24$ and did not meet Petersen's criteria for MCI. Participants underwent ^{1}H-MRS, genotyping and neuropsychological testing to assess general cognition, memory and attention/executive functions. Subjects were subdivided according to age (56 subjects <65 years and 56 subjects $=>65$ years) and APOE genotype (89 E3/E3 homozygotes and 23 E4 carriers). A 10.8 cm3 (2 x 2 x 2.7 cm) mid-sagital oblique posterior cingulate region ^{1}H-MRS voxel was prescribed with the long axis parallel to the parieto-occipital sulcus. Double-spin-echo (PRESS) spectra were acquired on a GE Twinspeed 3T MRI scanner with HDx technology, using an 8-channel phased array head coil, with 128 excitations acquired at TR = 1600 ms, TE = 30 ms. ^{1}H-MRS metabolite ratios were quantified automatically with vendor-supplied software. For ^{1}H-MRS analysis, the relative metabolite levels and ratios were determined for NAA, Cr, Cho, and mI. NAA is an amino acid thought to reflect general neuronal integrity/viability. Cho may reflect not only membrane turnover generally, but, in the context of AD, Cho may specifically reflect membrane turnover in acetylcholine neurons. Myoinositol plays an important role in cellular signal transduction through regulation of intracellular calcium, and is generally considered a marker of microglial and astrocyte activation that might be considered as a signal of neuronal inflammation. General Lineal Models (GLM) were used to examine the effect of APOE, age, and their interaction on ^{1}H-MRS metabolites, and Structural Equation Modeling (SEM) using SAS (GLM and CALIS procedures) was performed in order to determine causal relationships between those variables.

Results: GLM analysis showed that Cho/Cr ratios were found to be influenced significantly by APOE ($F_{1,\ 108} = 4.00$, $p = .05$), age ($F_{1,\ 108} = 3.86$, $p = .05$), and by the interaction between APOE and age ($F_{1,\ 108} = 6.86$, $p = .01$), demonstrating that older carriers of the e4 APOE allele had higher Cho/Cr ratios. mI/Cr ratios showed an independent effect of APOE ($F_{1,\ 108} = 5.37$, $p = .02$), a nearly significant effect of age ($F_{1,\ 108} = 3.16$, $p = .08$), and no effect of the interaction between APOE and age ($F_{1,108} = 1.20$, $p = .27$). No effects of APOE ($F_{1,\ 108} = .03$, $p = .85$), age ($F_{1,\ 108} = .00$, $p = .98$), nor an interaction between APOE and age ($F_{1,\ 108} = .02$, $p = .87$) were found on NAA/Cr ratios. The effect sizes for the comparison between older carriers of APOE e4 and younger APOE e3 homozygotes were in the high medium to large range (.7 for mI/Cr, .8 for Choline/Cr). SEM modeling showed that a general model, including both, direct and indirect (mediated through ^{1}H-MRS metabolites) effects of APOE, age and the interaction between them on cognition, fitted the data well. However, several individual paths were non-significant. By deleting non-significant paths, a final more parsimonious model, with an improved goodness of fit (Chi square = 15.06/df = 14/p = .37; General Fit Index = .96; Non-Normed Fit Index = .99; Comparative Fit Index = 1.00; Root Mean Square Error Aproximation = .03), showed that the interaction between APOE and age had a highly significant effect on mI/Cr, and this interaction showed a significant mediator effect on cognition through mI/Cr ratio. Furthermore, APOE and age (independently) also showed a direct effect on Cho/Cr ratio. As expected, age also had a direct effect on cognition.

Conclusions: This is the first study to find APOE effects on MRS metabolite ratios in a healthy aging control population. Specifically, Cho/Cr and mI/Cr ratios were found to be increased in older carriers of the e4 APOE allele. Additionally, path analysis confirmed that 1) the influence of APOE e4 status and older age on cognition was mediated through mI/Cr ratio; 2) higher Cho/Cr ratio was influenced by APOE, age, and the APOE/age interaction, but not related to cognition; 3) as expected age had a considerable detrimental effect on cognition. The finding of APOE x age effect through mI/Cr on cognition might suggest a signal implicating microglial neuroinflammatory processes that have been found in aging, AD neurodegeneration, and *in vitro* studies of APOE e4. Choline's role in membrane turnover has previously been supported, specifically in cholinergic neurons. Nevertheless, little is known about APOE interactions with cholinergic neurons. Speculatively, because APOE is associated with earlier age of onset of AD, it may consequently compromise cholinergic neurons known to be vulnerable to early AD pathology.

Keywords: 1H-MRS, Aging, APOE, & Cognition

Disclosure: J. Gomar, Nothing to Disclose; M. Gordon, Nothing to Disclose; P. Kingsley, Nothing to Disclose; A. Ulug, Nothing to Disclose; K. Jeremy, Nothing to Disclose; C. Conejero-Goldberg, Nothing to Disclose; P. Davies, Nothing to Disclose; T. Goldberg, **Part 1:** Dr. Goldberg has royalties for the use of the BACS test.

T101. Membrane Phospholipid Turnover in First Degree Relatives of Schizophrenia Subjects

Konasale Prasad*, Dhruman Goradia, Krishna Pancholi, Steven Goodnow, Brent Oliveros, Matcheri Keshavan, Vishwajit Nimgaonkar, Jeffrey Stanley

University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Background: First-degree relatives of schizophrenia subjects (HR) have about 10% risk of developing schizophrenia (SZ). We recently reported systematic differences in cortical surface area and thickness among adolescent offspring of SZ parents showing

reduced fronto-parietal gyral surface area along with increased parietal sulcal curvature and gyral cortical thinning compared to healthy subjects. Prospective follow up for 1 year showed shrinking of the total cortical surface area, especially in the bilateral frontal and occipital regions along with preservation of cortical thickness among offspring of schizophrenia parents whereas healthy subjects showed preserved or increased surface area and cortical thinning [would be helpful to add reference(s)]. In this study we examined membrane phospholipid turnover among offspring and siblings of schizophrenia subjects in comparison with early course schizophrenia and healthy subjects.

Methods: We acquired whole-brain, multi-voxel 3D ^{31}P CSI data at 3 Tesla on 98 subjects (SZ = 39, HR = 24, HC = 35). Mean age of subjects showed that SZ subjects (24.36 ± 6.94 years) did not differ from HR subjects (22.96 ± 3.73 years) but HR subjects were significantly younger than HC (26.97 ± 7.52 years)($p = 0.02$). The region of interest (ROI) included the individual right and left PFC, hippocampus, thalamus and superior temporal gyrus (STG). These regions were selected based on our prior observations of cross-sectional and longitudinal changes in cortical surface area and thickness among HR subjects (Prasad et al., 2008), and our diffusion tensor imaging study showing reduced fractional anisotropy in the frontotemporal and frontothalamic tracts (Prasad et al., 2012). Post-processing included shifting the superimposed 3D CSI grid relative to the anatomical images in order to place voxels in the specified ROI's. The ^{31}P signal of these voxels were then extracted and quantified in the time-domain (100% automated). The quantified metabolite levels, PME (PE + PC), PDE (GPC + GPE), phosphocreatine, adenosine triphosphate, dinucleotides and inorganic orthophosphate, were expressed as a mole % of the total signal. We used MANCOVA to examine the differences across the groups using age, sex and socioeconomic status as covariates and non-linear regression and curve fitting to examine the effect of age on the metabolites [SPSS V20 & Stata12].

Results: The main subject group term was significant with increased PDE levels in left hippocampus and left STG in patients compared to controls. HR subjects showed decreased PME in the right PFC and increased PDE in the right thalamus compared to controls. However, HR and schizophrenia subjects did not differ on PME and PDE in any of the VOI. However, we noticed a significant effect of age on the levels of PME and PDE in the right and left PFC and thalamus and a trend toward significance in the hippocampus among schizophrenia subjects. HR showed similar changes in the hippocampus and thalamus but not in the prefrontal cortex. HC did not show any effect of age within these regions. Age explained 36% of variance in PME ($F(2, 38) = 10.50$, $p = 0.0003$) and 30% of variance in PDE ($F(2, 38) = 7.87$, $p = 0.001$) in the right prefrontal cortex using a quadratic fit suggesting that the PME levels increased up to 25 years and then decreased after 30 years whereas PDE showed a reverse trend at the same ages. Left thalamus showed an opposite trend where PME decreased until about 25 years and then increased after 30 years ($F(2, 38) = 10.01$, $p = 0.0003$) with an $R^2 = 0.36$ and PDE increased at the same ages ($F(2, 38) = 3.09$, $p = 0.068$) with an $R^2 = 0.15$ with a quadratic fit. Among HR, only the right thalamus showed reduction in PME with no change in PDE with a quadratic fit ($F(2, 24) = 3.15$, $p = 0.06$, $R^2 = 0.22$). Hippocampus and superior temporal gyrus did not show such changes within any study group.

Conclusions: We observed a non-linear pattern of age-related change in membrane phospholipid turnover among subjects with SZ and first-degree relatives compared to healthy subjects that approximately corresponds to neurodevelopment. The differential pattern of changes in PME and PDE between prefrontal cortex and thalamus may suggest the timing of maturation of these regions since prefrontal cortices tend to show maturation much later in age. Healthy subjects not showing age-related changes such that this group might have completed early developmental phases before the age at recruitment. Longitudinal studies using MPL turnover rates as a predictor could identify individuals at higher risk for future conversion to psychosis.

Keywords: Psychotic disorders; Membrane Phospholipids; Magnetic Resonance Spectroscopy; Neurodevelopment; Familial High Risk

Disclosure: K. Prasad, Nothing to Disclose; D. Goradia, Nothing to Disclose; K. Pancholi, Nothing to Disclose; S. Goodnow, Nothing to Disclose; B. Oliveros, Nothing to Disclose; M. Keshavan, Nothing to Disclose; V. Nimgaonkar, Nothing to Disclose; J. Stanley, Nothing to Disclose.

T102. Cortical, Diencephalic and Midbrain Gray Matter Volume in Alcoholism Measured by VBM: Effect of Co-morbid Substance Abuse

Daniel W. Hommer*, Erica N. Grodin, Reza Momenan

National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland

Background: For many years we have noted that the majority of alcohol dependent patients seeking treatment at the NIH Clinical Center have, at some during their life, met DSM-IV criteria for substance use disorders in addition to alcoholism. In this report we used a Voxel-based morphometry (VBM) approach to compare regional brain volume differences between individuals with alcohol dependence and controls. We hypothesized that the alcohol dependent population would display large losses of gray matter in the frontal lobes, as has been reported in previous studies. Additionally we sought to investigate, we believe for the first time, regional differences between polysubstance abusing alcoholics and alcoholics who have never met DSM-IV criteria for any substance use disorder other than alcohol dependence. Since our previous work comparing overall gray matter forebrain volumes in 'pure' and substance abusing alcoholics did not find a significant difference between these groups, we tested the hypothesis that the groups would differ in regional gray matter density, but made no specific hypothesis about the direction of the difference.

Methods: Thirty-seven 'pure' alcoholics, 93 polysubstance abusing alcoholics, and 69 healthy controls underwent structural MRI scans using a 1.5T General Electric MRI scanner (General Electric, Milwaukee, WI) and a standard head coil. Whole-brain high-resolution coronal scans were collected using a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) pulse sequence with matrix 256 × 256 × 124, repetition time (TR) = 100 ms, echo time (TE) = 12 ms, field of view (FOV) = 24 cm, and voxel size of (0.9375x0.9375x2.0) mm^3. Structural data was analyzed with FSL-VBM, a voxel-based morphometry analysis software carried out with FSL tools. First, structural images were brain-extracted using BET. Next, tissue-type segmentation was carried out using FAST4. The resulting gray matter partial volume images were then aligned to MNI152 standard space using the affine registration tool FLIRT, followed by nonlinear registration using FNIRT, which uses a b-spline representation of the registration warp field. The resulting images were averaged to create a study-specific template (with equal number of patient and control subjects to avoid bias), to which the native gray matter images were then non-linearly re-registered. The registered partial volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, voxel wise GLM was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space. This approach is unbiased, in that it requires no *a priori* information about the location of these possible differences in the grey matter, and is not operator-dependent. It follows the optimized VBM protocol developed by Good and colleagues. All results are corrected for multiple comparisons (FWE correction) at a significance level $p < 0.01$.

Results: Alcoholic dependent inpatients (both with and without a history of DSM-IV substance abuse/dependence diagnosis) displayed significant gray matter volume reduction in the mesial surface of the frontal lobe and right temporal lobe compared to controls. In addition, 'pure' alcoholics exhibited a pattern of subcortical gray matter reduction involving the dorso-medial thalamus, the quadrigeminal plate, the mammilary bodies and periaqueductal gray compared to polysubstance abusing alcoholics. 'Pure' alcoholics and polysubstance abusing alcoholics did

not differ significantly in measures of cortical gray matter, liver function, and nutrition, or in estimated lifetime alcohol consumption.
Conclusions: These findings reinforce the accepted literature in regards to mesial frontal lobe gray matter volume reduction in alcohol dependence. However, our results unexpectedly show greater subcortical gray matter volume reduction in 'pure' alcoholics compared to polysubstance abusing alcoholics. This pattern of subcortical damage is very similar to the pattern seen in Wernicke-Korsakoff's Syndrome and may represent a spectrum of subcortical damage extending from classic Wernicke-Korsakoff's Syndrome to 'pure', but neurologically uncomplicated, alcoholism. Further research is needed to elucidate the exact cause of this pattern of atrophy and to determine what factors are responsible for the different patterns of gray matter reduction in 'pure' and polysubstance abusing alcoholics.
Keywords: Alcoholism, Voxel-based morphometry, MRI, Polysubstance abuse
Disclosure: D. Hommer, Nothing to Disclose; E. Grodin, Nothing to Disclose; R. Momenan, Nothing to Disclose.

T103. Functional Connectivity between Broca's Area and the Default Mode Network is Associated with Auditory Hallucinations: an FBIRN Study

Judith M. Ford*, Steven Potkin, Theo Van Erp, Brian J. Roach, Harshad Shanbhag, Adrian Preda, Ayse Belger, Vince Calhoun, Jessica Turner, Bryon Mueller, F. Birn, Daniel H. Mathalon

UCSF, San Francisco, California

Background: During rest, our minds wander, undirected. This allows us to experience unbidden memories of old conversations and imagine future exchanges. In normal people, these auditory percepts are tagged as coming from "self", but in people who hallucinate, they might be perceived as "voices", coming from external sources, or auditory verbal hallucinations. Analysis of neural activity during rest allows us to study what the brain is doing when allowed to wander. Connectivity between brain regions can be assumed when activity in the different regions is correlated. Accordingly, resting state connectivity analyses of functional magnetic resonance imaging (rs-fMRI) data allow us to assess the functional connectivity between brain regions as the mind is left to wander, and to draw conclusions about where the mind wandered. We assessed functional connectivity between brain regions typically active during rest (the default mode network), between regions typically active during auditory hallucinations, and between thalamus and cortex. Importantly, we asked whether connectivity between these regions was different in patients who tended to hallucinate.
Methods: We analyzed fMRI data from 183 patients with schizophrenia and 178 age-matched controls, during a 6-minute rest period, collected by the FBIRN consortium from 7 different sites across the country using 3T MRI scanners. Using a seed-based approach, we correlated the time-series in every voxel in the brain with time-series extracted from these seed regions of interest: (1) posterior cingulate/precuneus (PCC), a dominant node in the default mode network; (2) Wernicke's and Broca's areas, associated with the experience of AVH; and (3) thalamus (and its subregions) because of thalamo-cortical dysfunction characteristic of schizophrenia.
Results: A general pattern emerged: schizophrenia patients had greater connectivity *between* subcortical and cortical regions, while controls had greater connectivity *within* cortical and *within* subcortical regions. Using a thalamus seed, patients had greater connectivity between thalamus and auditory cortex, and controls had greater connectivity within the thalamus itself. This pattern was maintained when specific nuclei within the thalamus were used as seeds. With the Broca's seed, schizophrenia patients had greater connectivity with the default mode network, and controls had greater connectivity with frontal lobe areas, including areas involved in speech/thought production (Broca's area) and executive control (dorsal lateral prefrontal cortex). Patients who experienced "voices commenting", a prominent feature of auditory hallucinations, had greater connectivity between Broca's area and the default mode network.
Conclusions: We suggest that during rest, verbal thoughts emerge through activity in Broca's area. We further suggest that these thoughts are largely under the control of frontal, executive regions in healthy controls, while in patients, they are associated with activity in the default mode network, especially in patients who hear voices commenting.
Keywords: Schizophrenia Auditory hallucinations Default mode network fMRI Connectivity
Disclosure: J. Ford, **Part 1:** My husband is a consultant to Bristol Meyers Squibb; S. Potkin, **Part 1:** Bristol-Myers Squibb, Eisai, Inc., Eli Lilly, Forest Laboratories, Genentech, Janssen Pharmaceutical, Lundbeck, Merck, Novartis, Organon, Pfizer, Roche, Sunovion, Takeda Pharmaceutical, Vanda Pharmaceutical, **Part 2:** Lundbeck, Merck, Novartis, Sunovion, **Part 3:** Lundbeck, Merck, Novartis, Sunovion, **Part 4:** Amgen, Baxter, Bristol-Myers Squibb, Cephalon, Inc., Eli Lilly, Forest Laboratories, Genentech, Janssen Pharmaceutical, Merck, Novartis, Otsuka, Pfizer, Roche, Sunovion, Takeda Pharmaceutical, Vanda Pharmaceutical, NIAAA, NIBIB, NIH/NCRR, University of Southern California, UCSF, UCSD, Baylor College of Medicine; T. Van Erp, Nothing to Disclose; B. Roach, Nothing to Disclose; H. Shanbhag, Nothing to Disclose; A. Preda, **Part 1:** Boehringer-Ingelheim Advisory Board, **Part 2:** University of California, Irvine; A. Belger, Nothing to Disclose; V. Calhoun, Nothing to Disclose; J. Turner, Nothing to Disclose; B. Mueller, Nothing to Disclose; F. BIRN, Nothing to Disclose; D. Mathalon, **Part 1:** I consult to BMS.

T104. Regional Brain Volume in ADHD and Its Relationship to Ataxia and Intrasubject Variability

Eve Valera*, Thomas Zeffiro, Rebecca Spencer, Nikos Makris, Stephen Faraone, Larry Seidman, Jeremy Schmahmann

Harvard Medical School/Massachusetts General Hospital, Charlestown, Massachusetts

Background: Motor coordination problems in ADHD have long been recognized in ADHD, and studies have found that up to 50% of ADHD children have motor difficulties. These difficulties can have a detrimental impact on their lives. Although these issues are addressed in a literature for ADHD children, there do not appear to be any analogous reports regarding detailed motor assessment of coordination in ADHD adults or any examination of how these motor abnormalities may relate to structural brain volume or other behavioral variables.
Methods: Using a modified version of the International Cooperative Ataxia Rating Scale (MICARS), we obtained an objective assessment of ataxia severity in 22 ADHD adults and 22 matched controls. We used voxel based morphometry incorporating the SUIT cerebellar spatial normalization technique to examine ataxia scores in relation to regional brain volumes. We also used a tapping task to examine ataxia scores in relation to intrasubject variability.
Results: Relative to controls, ADHD adults showed significantly higher scores for total ataxia, posture and gait disturbances, and limb/kinetic measures. Ataxia scores were negatively correlated with regions in middle and superior frontal gyri as well as the posterior cerebellum (trend level). Ataxia scores were also positively correlated with tapping intrasubject variability, which was also higher in the ADHD adults. Total and clock, but not motor, variance were associated with ataxia scores.
Conclusions: These data show that motor abnormalities in ADHD persist into adulthood and can be detected by clinical motor examination. These data also show that ataxia is associated with localized volume reductions in frontal gyri, with a trend in a region of the secondary motor representation of the cerebellum.

Associations between frontal regions and ataxia are consistent with previous reports implicating regions of the frontal cortex in ataxia. Finally, measures of ataxia are related to clock but not motor intrasubject variability, providing additional support for timing abnormalities contributing to the clinical phenomenology of ADHD. Overall, these findings provide additional evidence for the involvement of frontocerebellar abnormalities in the pathophysiology of ADHD.

Keywords: ADHD, ataxia, MRI, intrasubject variability, frontocerebellar

Disclosure: E. Valera, **Part 1:** Self: Galenea Inc: Honoraria for talk, Spouse: Galenea, Inc.: paid consultant. Bristol-Myers Squibb: paid consultant, **Part 4:** Spouse: Research and Development Grant from Galenea, Inc.; T. Zeffiro, Nothing to Disclose; R. Spencer, Nothing to Disclose; N. Makris, Nothing to Disclose; S. Faraone, **Part 1:** Shire, Akili, Alcobra, **Part 4:** Shire; L. Seidman; J. Schmahmann.

T105. White Matter Trajectories from Childhood into Late Adulthood

Bart D. Peters*, Philip R. Szeszko, Toshikazu Ikuta, Kimberly Cameron, Patricia Gruner, Pamela DeRosse, John Cholewa, Anil Malhotra

Zucker Hillside Hospital; Feinstein Institute for Medical Research, Glen Oaks, New York

Background: Diffusion tensor imaging (DTI) studies have shown ongoing maturation of brain white matter (WM) tracts from childhood into adulthood, followed by decline into old age. Few studies have examined large samples across the lifespan, and explored specific nonlinear models of these trajectories.

Methods: DTI was performed at 3T in 296 healthy subjects aged 8-68 years (mean 29.6 years). Seven bilateral projection and association WM tracts and the genu and splenium of the corpus callosum (CC) were segmented in native space using probabilistic tractography in FSL's diffusion toolbox (www.fmrib.ox.ac.uk/fsl/). Relationships between age and fractional anisotropy (FA), a putative marker of WM integrity, were examined using Poisson and quadratic models, based on previous findings. In addition, cognitive performance was assessed across several domains.

Results: Five WM tracts showed significant FA increases from childhood into early adulthood (cingulum, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and genu of the CC), followed by gradual decline into late adulthood. FA values of these tracts peaked between 25 and 40 years of age where the cingulum matures last. The Poisson model fitted these trajectories best, as determined with Akaike's information criterion. The corticopontine tract, uncinate fasciculus, anterior thalamic radiation and splenium of the CC showed little age effects. There were no significant trajectory differences between males and females.

Conclusions: These data highlight increasing connectivity in association and commissural WM tracts from childhood into early and middle adulthood, followed by gradual decline into late adulthood. These findings may have relevance for psychiatric disorders that have implicated neurodevelopmental white matter abnormalities in their pathogenesis.

Keywords: white matter, adolescence, development, aging, diffusion tensor imaging

Disclosure: B. Peters, Nothing to Disclose; P. Szeszko, Nothing to Disclose; T. Ikuta, Nothing to Disclose; K. Cameron, Nothing to Disclose; P. Gruner, Nothing to Disclose; P. DeRosse, Nothing to Disclose; J. Cholewa, Nothing to Disclose; A. Malhotra, **Part 1:** Genomind (scientific advisory board), Shire (scientific advisory board), Eli Lilly (consultant grant/research support), Sunovion Pharmaceuticals Inc. (speaker's bureau), Schering-Plough/Merck (speaker's bureau), Abbott (grant support), **Part 2:** Genomind, **Part 4:** Abbott.

T106. Stimuli Presentation Modification Improves Diagnostic Accuracy at the Individual Level for Functional MRI Detection of Deception

Steven Laken, Andrew Lai, Kevin Johnson, Paul Morgan, Kimberly Levine, Michael Fernald, Ketan Patel, Kristy Hass, Jennifer Cahill, F. Andrew Kozel*

University of South Florida, Tampa, Florida

Background: Functional neuroimaging studies have largely relied on group results to investigate the function of the brain. For diagnostic purposes, however, valid individual results are required – but that has been problematic for functional neuroimaging. The difficulty with achieving valid individual results could be due to either inadequate power of individual analyses (i.e., the signal to noise ratio is too low) or the variability of brain circuitry between participants. One area of research that has successfully demonstrated valid individual results that has been replicated in multiple settings is functional MRI (fMRI) detection of deception. This paradigm offers the ability to investigate whether increasing the power of a test using a mixed-design question format (Mixed-Design) versus a standard event related question format (Event-Related) could significantly improve the accuracy of a neuroimaging diagnostic test. Using a randomized cross over design, testing whether the Mixed-Design format produced a higher rate of accuracy to detect deception than the standard Event-Related question format previously employed was performed on an independent sample of healthy participants. Addressing this question could also address the question of whether the difficulty with individual reliability with fMRI is primarily due to individual variations in brain circuit function or conversely to inadequate signal to noise of the technology being employed.

Methods: This study was submitted and accepted by the New England Institutional Review Board. Healthy subjects not taking any medications were recruited in the greater Boston area by word-of-mouth and newspaper advertisements. Thirty-six subjects were consented, screened, and taken through a mock-crime deception paradigm. Participants "stole" either a watch or a ring and were instructed to lie about stealing while being scanned. The participants were then imaged twice on the same day using a 1.5T Siemens scanner. One scanning run utilized the Mixed-Design question-format and the other utilized the Event-Related question format. Participants were randomized to the order of which question format (i.e., Mixed-Design or Event-Related) would be performed first in the fMRI scanner. The analysis of the fMRI data was performed with Statistical Parametric Mapping software (SPM2, Welcome Department of Cognitive Neurology, London, United Kingdom—run on Matlab). Preprocessing and statistical analysis of the fMRI data used the same SPM2 procedures and settings for both the Event-Related and Mixed-Design. The results independently obtained by SJL and FAK were locked and then compared. In addition, the results were subsequently completely re-run by AL with SPM8 to confirm that the newer analysis software did not change the results of the calls of when the participants were being deceptive.

Results: For the 31 participants analyzed, they ranged in age from 18-46 years with a mean of 25.9 years (s.d. 6.83) and median of 25.0 years. Sixteen participants were female (52%). Three were Asian, two were from African descent, 24 were Caucasian, and two reported being Hispanic. Fifteen subjects took the watch and sixteen subjects took the ring. The randomization resulted in 15 participants starting with the Event-Related question format and 16 starting with the Mixed-Design question format. The Mixed-Design question format with the greater power (correctly called 30/31 for an accuracy of 97%) significantly (McNemar's Statistic, $p = 0.02$) improved the accuracy rate to detect deception compared to the standard Event-Related question format (correctly called 23/31 for an accuracy of 74%). The two investigators (SJL and FAK) using SPM2 had identical calls for both Event-Related and Mixed-Design question format groups. AL reran the analysis with updated parameters in SPM8 which also resulted in changing of the peristimulus timing. AL obtained the same results except one of the

Event-Related calls that was previously incorrect became correct. Rerunning SPM2 with the same peristimulus time change resulted in the same results as SPM8.

Conclusions: These results demonstrate that increasing the power of a neuroimaging methodology can increase the accuracy of an fMRI diagnostic test. This improved accuracy was found while testing the same participants using the same scanner and acquisition parameters. This provides support to the concept that the difficulty in identifying reliable results at the individual level of analysis for fMRI is more a function of low signal to noise versus individual differences in brain functional circuitry. In addition, the greater the power of the methodology to detect a difference, the more robust the results obtained at the individual level. As fMRI technology moves to making current or future predictions at the level of the individual in various areas of investigation, these results are encouraging. As the power of the technology improves, so can the accuracy of the results obtained. Further work is required to test these improvements in technology in a broader sample of participants and in diverse testing scenarios.

Keywords: fMRI, diagnostic test, individual level of analysis, detect deception

Disclosure: S. Laken, **Part 1:** Cephos Corp has worked with Vertex Pharmaceuticals, Axela, Inc., YOUology, Xceed Molecular and Chronic Pain Diagnostics Inc, **Part 2:** I am employed by Cephos Corp. and have equity in Cephos Corp, **Part 3:** I am employed by Cephos Corp.; A. Lai, Nothing to Disclose; K. Johnson, Nothing to Disclose; P. Morgan, **Part 1:** Member of Trial Steering Group & Radiology Committee for F. Hoffmann-La Roche's HERBY study (BO25041); K. Levine, Nothing to Disclose; M. Fernald, Nothing to Disclose; K. Patel, Nothing to Disclose; K. Hass, Nothing to Disclose; J. Cahill, Nothing to Disclose; F. Kozel, **Part 1:** Royalty/patent, other income: patents as an inventor through the Medical University of South Carolina on fMRI Detection of Deception, patents pending for Guided rTMS Inhibition of Deception, Optimizing VNS dose with rTMS, Other: Unpaid scientific consultant to Cephos Corp, **Part 4:** Current Research and/or salary Support: 03/2011 – 12/2013 DM090122, (Hart PI) Department of Defense "Novel Treatment of Emotional Dysfunction in PTSD" Role: Co-investigator, 09/30/10 – 06/30/14 1 U01MH092221-01, (Trivedi PI), NIMH "Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC)" Role: Co-investigator, no salary support since July 2011, Past Research and/or Salary Support: the National Institute of Mental Health K23 NIMH 5 K23 MH070897-02, Role: PI; NIH/NCRR 5 UL1 RR024982-02 Packer (PI) Role: Pilot Study PI; Neuronetics Grant-in-kind support for supplies and use of equipment; the Defense Academy for Credibility Assessment (formerly the Department of Defense Polygraph Institute), Cephos Corp., Stanley Medical Research Institute, Cyberonics (Treatment studies D01, D02, D04, AN01) 2001-2005; Glaxo Smith Kline (Interleaved TMS-fMRI) 2002-2003.

T107. A Mechanism of Ventricular Enlargement in an Alcohol Binge Model

Natalie M. Zahr*, Edith Sullivan, Adolf Pfefferbaum

Stanford University, Stanford, California

Background: Ventricular enlargement, readily visualized and quantified on magnetic resonance imaging (MRI), is a common marker of CNS insult, disease, and aging. Although ventricular enlargement is typically presumed to reflect atrophy of surrounding brain regions, its mechanism is unknown and may be specific to the condition under investigation. In the case of excessive alcohol consumption, profound yet completely reversible ventriculomegaly was previously observed in rats exposed to high doses of ethanol (EtOH) administered under a binge-like treatment schedule.

Methods: ere, multimodal MR, incorporating structural MRI, MR spectroscopy (MRS), and MR diffusion tensor imaging (DTI), was used in rats exposed to the same EtOH binge treatment protocol to determine the mechanism of ventricular enlargement.

Results: During intoxication, MRI showed pronounced ventricular expansion but did not reveal volume changes in dorsal or ventral hippocampi, caudate-putamen, or thalamus. MRS showed increases in choline-containing compounds (Cho) and decreases in N-acetylasparate (NAA) and tissue water T2. DTI focused on measurement of freely diffusing water molecules in gray matter structures showed decreased diffusivity selective to the thalamus. All MR parameters returned to baseline with 7 days of recovery.

Conclusions: The absence of quantifiable tissue volume reductions in brain regions adjacent to the ventricles and rapid recovery argue against atrophy as a mechanism of ventricular expansion. The decrease in tissue water T2 measured with MRS, diffusivity in thalamic tissue measured with DTI, and ventricular enlargement measured with MRI together suggest movement of water from tissue into ventricles. A role for NAA as a molecular water pump, carrying NAA-obligated water out of neurons, is proposed. The increase in Cho implies cell membrane disruption, accounted for by membrane compression as water diffuses out of shrinking cells. Together, these data support a model of rapidly shifting fluids from brain parenchyma to ventricles during acute binge EtOH intoxication and movement of fluid back to parenchyma during recovery.

Support: AA005965, AA013521-INIA, AA017168

Keywords: ventricular enlargement, ethanol, diffusion tensor imaging, gray matter, water diffusion

Disclosure: N. Zahr, Nothing to Disclose; E. Sullivan, Nothing to Disclose; A. Pfefferbaum, Nothing to Disclose.

T108. Sex Differences in the Effect of Childhood Emotional Abuse on Hippocampal Volume

Pamela DeRosse*, Erin Samplin, Toshikazu Ikuta, Anil Malhotra, Philip R. Szeszko

Zucker Hillside Hospital, Glen Oaks, New York

Background: Childhood maltreatment is a major risk factor for psychiatric illnesses. Several lines of evidence suggest that childhood maltreatment results in substantial alterations in the hypothalamic-pituitary-adrenal (HPA) axis responsiveness which may contribute to the development of psychiatric illness. This effect is believed to be mediated by impaired hippocampal development as considerable data have shown that the hippocampus is highly susceptible to stress and involved in the regulation of the HPA-axis Moreover, numerous studies have shown associations between decreased hippocampal volume and psychiatric illness including mood, anxiety, substance abuse, psychotic, and personality disorders. However, because most studies seeking to assess the consequences of childhood maltreatment on hippocampal volume are conducted in patient samples, it is unclear whether the observed reductions are related to the maltreatment or the psychiatric illness itself. Therefore, the present study sought to assess the relationship between common types of childhood maltreatment and hippocampal volumes in healthy adults with no history of psychiatric illness.

Methods: Sixty-eight healthy adults (mean age = 36.88 ± 15.52) were recruited from the community and comprehensively assessed for an ongoing study on subclinical psychopathology. Retrospective childhood maltreatment data were collected using the 28-item Childhood Trauma Questionnaire, which assesses 5 domains of childhood maltreatment including: physical abuse (PA), physical neglect (PN), emotional abuse (EA), emotional neglect (EN) and sexual abuse (SA). Participants were split into maltreatment positive and negative groups on each subscale based on whether or not they endorsed any history of the specific type of maltreatment. Sexual abuse and physical neglect were excluded from analyses due to low and high frequency of endorsement, respectively. Magnetic Resonance Imaging (MRI) exams were conducted on a 3T GE system. Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). Preliminary analyses compared the maltreatment + and – groups on a series of demographic characteristics. The primary analyses utilized a series of

2-Factor univariate ANOVA's were carried out to assess the relationships between history of maltreatment (EA, EN, PA) and sex on total hippocampal volume. In each analysis age was entered as a covariate.
Results: Preliminary analyses revealed no differences between the EA+ and EA− group were observed on sex, age, race, general intelligence (*g*) or socioeconomic status. In the primary analysis, no main effects of EA history or sex were observed. However, a significant interaction between EA and sex was observed ($p = 0.01$). Specifically, a positive history of emotional abuse was associated with significant decreases in total hippocampal volume in males only. No significant differences in hippocampal volume were observed for EN or PA although significant differences were observed in the average age of participants in these groups. Specifically, those participants who endorsed a history of EN and PA were significantly older than those who did not.
Conclusions: These results suggest that the effects of childhood maltreatment on hippocampal volume in adult subjects with no history of an axis I disorder may be dependent on sex. The findings suggesting an association between a history of EA and decreased hippocampal volume in males but not females contrast with prior findings in psychiatric samples in which higher rates of trauma are associated with global decreases in hippocampal volume in psychiatric illnesses, particularly depression and anxiety, that are more common in females.
Keywords: Childhood Trauma MRI Hippocampus Emotional Abuse Healthy Controls
Disclosure: P. DeRosse, Nothing to Disclose; E. Samplin, Nothing to Disclose; T. Ikuta, Nothing to Disclose; A. Malhotra, Nothing to Disclose; P. Szeszko, Nothing to Disclose.

T109. A Study of Glutamatergic Function in Adolescent Males with High-functioning Autistic Disorder Using Magnetic Resonance Spectroscopy: A Pilot Study at 4T

Gagan Joshi*, Rachel Goldin, Dave Crowley, Scott Lukas, Atilla Gonenc

Massachusetts General Hospital, Boston, Massachusetts

Background: Dysregulation in glutamatergic activity has been hypothesized in the pathophysiology of autism spectrum disorders (ASDs; McDougle, 2002). Brain glutamate (Glu) activity has been measured in combination with glutamine (Gln) and gamma-aminobutyric acid (GABA) (Glu + Gln + GABA designated as Glx) by proton magnetic resonance spectroscopy (^{1}HMRS) in individuals with ASDs. Lower levels of Glx are observed in white and grey matter (GM) in children with ASDs (DeVito et al., 2007). On the contrary, in adults with ASDs, Glx levels are found to be higher in the amygdalo-hippocampal region (Page et al., 2006) and decreased in the right anterior cingulate cortex (ACC; Bernardi et al., 2011). Taken together, previous ^{1}HMRS studies in autism suggest Glx dysregulation in various regions, including regions implicated in autism (i.e., medial temporal lobe (MTL) and ACC). As the Glu concentration in previous ^{1}HMRS studies is assessed in combination with Gln and GABA, the Glx findings cannot be attributed only to Glu. Thus, spectroscopic quantification of Glu without Gln and GABA is essential for precise examination of the glutamatergic activity in individuals with autism. The primary aim of our study is to measure Glu levels in ASD youth of normal intelligence as compared to healthy controls. We focused on two regions, the bilateral MTL region, including amygdala and hippocampus, and the ACC, both of which have been implicated in the pathophysiology of autism.
Methods: Participant Characterization*: Fourteen subjects (7 ASD and 7 age-, sex-, and IQ-matched healthy comparison subjects) participated. All participants were right-handed males; age 12 to 17 years old. The DSM-IV based diagnosis of ASD was established by a comprehensive psychiatric evaluation conducted by a board-certified psychiatrist experienced in evaluating ASDs (GJ). Full-scale IQ was determined with the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence Scale (Wechsler, 1999). At the time of scanning, 3/7 ASD participants were medication naïve. Imaging*: *Data Acquisition* - Proton spectra were acquired at 4T using a two-dimensional J-resolved (2D-JPRESS) MRS protocol. An 8 cc single voxel was placed in ACC along the midline such that the inferior edge of the voxel was parallel to the descending surface of the corpus callosum, as determined by T1 images used also for tissue segmentation. Then 3.375 cc single voxels were placed bilaterally in left and right MTL staying clear of the tip of the temporal bone to avoid shimming problems. Data were collected in 12 TE- stepped spectra with the echo-time ranging from 30 to 250 ms in 20 ms increments, with TR = 2 s, averages = 16 (for ACC) and 32 (for MTL), scan duration = 7 minutes (for ACC) and 13 minutes (for MTL). Spectral analysis was conducted by LCModel package (version 6.2-1F). *Data Processing*–After the 2D-JPRESS dataset was resolved into a series of one-dimensional spectra where each spectrum was modeled and fitted with GAMMA simulated (Smith et al., 1994) J-resolved basis sets, Glu levels were derived from the total integral across the J-series. Glu T2 relaxation time was obtained from the raw peak versus TE decay curve fitted with Levenberg-Marquardt algorithm using an exponential decay function (for Glu T2) convoluted with a polynomial function (for Glu J-coupling) which was obtained from the GAMMA simulation with previously measured spectral parameters (Govindaraju et al., 2000).
Results: Seven ASD participants (mean age: 14 ± 1.8 years; age range: 12-17 years) with intact intellectual capacity (mean IQ: 108 ± 14.26; IQ range: 85-127) were suffering from autistic disorder and psychiatric conditions (anxiety disorder = 3; anxiety disorder and ADHD = 3; mood disorder = 1). The ASD and control groups did not differ significantly in demographic characteristics. Paired *t*-test results indicate significantly increased Glu in the ACC of ASD versus control subjects (1.43 ± 0.20 versus 0.96 ± 0.18; $p = 0.01$), a trend for lower Glu in the right MTL (0.98 ± 0.06 versus 1.21 ± 0.20; $p = 0.06$), and Glu not statistically different between the groups in the left MTL (0.72 ± 0.08 versus 0.89 ± 0.16; $p = 0.1$).
Conclusions: Our findings of increased Glu levels in the ACC region and normal levels in the MTLs in high-functioning adolescent males with autistic disorder suggest over-activity of Glu in adolescents with autism. Clinical limitations of this study due to small sample size include the inability to examine medication effects, effect of other metabolites, and Glu association with phenotypic correlates. Imaging limitations include that T1 relaxation was not taken into account and that all resonance groups of Glu were assumed to have the same relaxation times. Despite these considerations, these preliminary results provide evidence that glutamatergic hyperactivity may be important in the pathophysiology of ASDs and should be replicated in a larger sample of subjects. If Glu contributes to the pathophysiology of ASDs, it is reasonable to suggest that agents modulating Glu may have some utility in its treatment. These results indicate that measurement of T2 values for *in vivo* Glu was feasible using multi-echo J-resolved MRS and a multi-echo J-resolved MRS data acquisition and analysis method resulted in good separation of the overlapping J-coupled metabolite resonances of Glu and Gln in ACC and MTLs, regions historically considered difficult to conduct MRS.
Keywords: autistic disorder, glutamate, youth
Disclosure: G. Joshi, **Part 1:** Research support (Site PI): Forest Research Laboratories, Duke University, Research support (Sub-investigator): Shire, Department of Defense, Schering-Plough Corporation, Eli-Lilly, Johnson & Johnson Pharmaceutical Research and Development; R. Goldin, Nothing to Disclose; D. Crowley, Nothing to Disclose; S. Lukas, Nothing to Disclose; A. Gonenc, Nothing to Disclose.

T110. Intrinsic Connectivity Abnormalities in Social Anxiety

Jennifer Blackford*, Jacqueline Clauss, Suzanne Avery, Ross VanDerKlok

Vanderbilt University, Nashville, Tennessee

Background: Social phobia is a common, chronic, and disabling disorder affecting 1 in 10 Americans. Social inhibition is a key

component of social anxiety and reflects underlying heritable trait differences. While the amygdala has been identified as a key neural substrate of social inhibition, little is known about the underlying neurocircuitry. Intrinsic connectivity methods provide a unique insight into fundamental structural and functional brain circuitry. Here we take a dimension approach to understanding anxiety by examining the relationship between social inhibition and intrinsic connectivity of the amygdala.
Methods: Intrinsic connectivity ('resting state') fMRI data were collected in 40 young adults who ranged from high to low in social inhibition. Three amygdala subnuclei seeds were created based on a standard probabilistic atlas. Connectivity was estimated between the three amygdala subnuclei and the whole brain. Cluster-based thresholds were used to correct for multiple corrections (family-wise corrected $p < .05$).
Results: Social inhibition was significantly associated ($p < .05$, corrected) with decreased connectivity between amygdala subnuclei and multiple prefrontal brain regions. The patterns of decreased connectivity were specific to each subnucleus. Individuals with higher social inhibition had decreased connectivity between: 1) the centromedial amygdala and dorsal anterior cingulate; 2) the superficial amygdala and both the rostral anterior cingulate cortex and orbitofrontal cortex; and 3) between the basolateral amygdala and middle frontal gyrus.
Conclusions: With this novel dimensional approach we have demonstrated that social inhibition—a key component of social anxiety—is associated with decreased connectivity between amygdala subnuclei and multiple prefrontal cortical regions. These findings demonstrate that social inhibition is associated with altered brain function at rest, in the absence of any social triggers. Importantly, altered amygdala connectivity with prefrontal cortical regions involved in emotion regulation, suggests that trait differences in intrinsic connectivity may be a mechanism by which social inhibition leads to social anxiety. Finally, these findings suggest a promising avenue for the development of new treatments for social anxiety that focus on strengthening amygdala-prefrontal cortical connectivity.
Keywords: connectivity; social anxiety; social inhibition; resting-state; fmri
Disclosure: J. Blackford, Nothing to Disclose; J. Clauss, Nothing to Disclose; S. Avery, Nothing to Disclose; R. VanDerKlok, Nothing to Disclose.

T111. Brain Response to "Unseen" Cannabis Cues among Cannabis-dependent Individuals

Reagan Wetherill*, Julian Bender, Kanchana Jagannathan, Yin Li, Charles P. O'Brien, Anna Rose Childress, Teresa R. Franklin

University of Pennsylvania, Philadelphia, Pennsylvania

Background: Substance dependence is commonly associated with enhanced reactivity to drug cues. Many drug abuse theories suggest that drug-related cues maintain and contribute to drug use and relapse. Exposure to drug-related cues, such as seeing one's drug of choice or associated paraphernalia, triggers conscious desire for the drug and activation of brain structures involved in incentive motivation and reward. In fact, our previous findings among cocaine dependent patients indicate that even when drug cues are presented entirely outside of conscious awareness (i.e., "unseen"), they can have profound effects on the brain's reward circuitry. It remains unknown, however, whether unseen cues elicit a similar neural response among cannabis-dependent individuals. Based on our previous findings (Childress et al., 2008), we hypothesize that cannabis-dependent individuals will show brain activation in reward regions, including the medial orbitofrontal cortex (mOFC), ventral striatum (VS), hippocampus, amygdala, anterior cingulate cortex (ACC), and insula when presented with "unseen" cannabis cues.
Methods: Nine (9) treatment-seeking cannabis-dependent individuals (4 female) completed an fMRI session that included a "fast" event-related design backward masking task used to examine brain response to "unseen" (backward masked) cannabis cues. Stimuli were presented in randomized jittered order with cannabis cues presented for 33 msec and followed immediately by a neutral picture of 466–467 msec (the mask) for a total 500 msec of visual stimuli. Participants were asked to rate their desire for marijuana immediately prior to and following the task. After slice-timing correction of the images, statistical mapping software (SPM8) was used for image realignment, smoothing with a 3-D 9 mm isotropic Gaussian kernel, and normalization into the Montreal Neurological Institute 152 averaged template. The General Linear Model with a canonical HRF as the basis function was used for pre-planned contrasts (cannabis vs. neutral) at the individual and group level using an *a priori* reward-related regions of interest (ROI) mask. The ROI mask is based on our cue-reactivity research (Childress et al., 2008; Franklin et al., 2007; 2009; 2011) and included mOFC, VS, hippocampus, amygdala, ACC, and insula. The ROI mask was created using the Harvard–Oxford probabilistic anatomical atlas provided with FMRIB Software Library (FSL).
Results: Consistent with our prediction, cannabis-dependent individuals show increased brain activation in reward-related regions, specifically the mOFC, VS, hippocampus, amygdala, ACC, and insula (p-uncorrected $< .001$), to unseen cannabis cues of only 33 msec duration. The "unseen" cues did not trigger conscious craving (pre- versus post-craving *scores* $p = 0.65$).
Conclusions: We demonstrate, for the first time, reward-related brain activation by unseen cannabis cues among cannabis-dependent individuals. These findings extend our previous study showing brain reward circuitry responds to cocaine cues presented outside awareness. Further, results provide additional support for the idea that brain response to reward cues outside of conscious awareness may represent a potential vulnerability for addictive behaviors.
Keywords: Cannabis, Marijuana, Cues, Neuroimaging, Reward
Disclosure: R. Wetherill, Nothing to Disclose; J. Bender, Nothing to Disclose; K. Jagannathan, Nothing to Disclose; Y. Li, Nothing to Disclose; C. O'Brien, **Part 1:** Occasional consultations for Alkermes Inc.; A. Childress, Nothing to Disclose; T. Franklin, Nothing to Disclose.

T112. Impact of Genetic Risk for Bipolar Disorder on Emotion Regulation Circuitry in a Population of Symptomatic Youth

Danella Hafeman*, Genna Bebko, Michele A. Bertocci, Henry Chase, Susan Perlman, Amanda Hinze, Mary Kay Gill, Christine Demeter, Vaibhav Diwadkar, Jeffrey Sunshine, David A. Axelson, Boris Birmaher, Robert Kowatch, Robert L. Findling, Mary L. Phillips

Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Background: Bipolar Disorder (BD) is highly heritable, and children with a parental history of mania (PHM) represent a population "at risk" for the development of this disorder. Family history of BD has been associated with a number of neuroimaging abnormalities, particularly in neural circuitry involving emotion regulation. An improved understanding of these abnormalities, and how they evolve over the neurodevelopmental trajectory, might shed light on the underlying pathophysiology of BD. The current study assessed the impact of PHM on fMRI measures in a clinical population of youth, preferentially selected based on symptoms of mania and mood dysregulation. We tested the hypothesis that PHM + youth (relative to PHM- youth and healthy controls) would show alterations in amygdala function, as well as prefrontal areas involved in implicit emotion regulation, particularly the orbitofrontal cortex (OFC, BA 11/47) and ventral anterior cingulate cortex (ACC).
Methods: Neuroimaging data were collected on a subset of the subjects recruited for the Longitudinal Assessment of Manic Symptoms (LAMS) study. This clinical sample of youth was preferentially recruited according to their score on a screen for

elevated symptoms of mania (ESM); however, only a minority met criteria for bipolar spectrum disorders at baseline. The Family History Screen was administered at baseline to determine parental history of psychiatric illness and manic symptoms. The current study analyzed available neuroimaging data for PHM+ youth (n = 19), as well as a PHM- sample (n = 19) that was matched on gender, age, and site; a group of healthy controls (HC) (n = 20) were included for comparison. An emotional dynamic faces task was used to assess implicit processing of emotional stimuli. Region of interest (ROI) analyses were conducted on the amygdala, OFC, and ACC, comparing the three groups (PHM+, PHM-, and HC) on emotions vs. shapes. Whole brain analyses were also conducted. Finally, preliminary analyses of psycho-physiological interaction (PPI) were conducted to assess functional connectivity, using an amygdala seed. Initial analyses were conducted using SPM8; data were then extracted into SAS 9.2 to adjust for potential confounders (age, gender, IQ, and clinical measures).

Results: The average age of the subjects was 13.7 years old, and the majority (35/56) were male. The omnibus condition comparing all emotions vs. shapes across the three groups showed significant clusters in OFC (corrected $p < 0.05$) and ventral ACC (corrected $p < 0.05$), but not amygdala. Findings in the OFC were driven by differences in the angry vs. shapes condition, where PHM+ showed increased activation relative to PHM-youth in bilateral OFC (corrected $p < 0.05$). Findings in the ACC were driven by differences in the fear vs. shapes condition, with decreased activation in PHM+ relative to PHM- (corrected $p < 0.05$). Interestingly, activation patterns in the HC were similar to the PHM+ in bilateral OFC, but similar to PHM- in ventral ACC. Whole brain analyses showed a pattern of increased activation in HC relative to PHM+ (corrected $p < .01$) in right dorsolateral prefrontal cortex (in the angry condition) and diffuse midline structures (in the fear condition). No group differences were observed in the happy or sad conditions, in either ROI or whole brain analysis. PPI analysis indicated that connectivity between amygdala and inferior frontal gyrus increased during the anger condition in PHM+ (relative to PHM-) youth (corrected $p < .05$). Adjustment for age, gender, IQ, race, and ESM did not alter results. To test for medication effects, analyses were repeated in subsets of youth who were free of each medication class (antipsychotics, antidepressants, and stimulants); findings did not change, meaning that they were unlikely to be due to medication. Effects of PHM also persisted after removing subjects with bipolar spectrum disorders, thus indicating that results were not driven by these individuals.

Conclusions: In this sample of symptomatic youth, PHM is associated with alterations in activation of OFC and ventral ACC during a task involving implicit emotion processing. Both ROI and whole brain analyses indicate that healthy controls generally have increased activation in prefrontal structures during the angry and fearful conditions, relative to the clinical sample (both PHM+ and PHM-). However, the pattern of decreased activation differs with regard to PHM. While PHM+ youth have decreased ACC activation (relative to both PHM- and HC groups) during the fearful task, PHM- youth have decreased OFC activation (relative to both PHM+ and HC groups) during the angry task. This finding, along with the increased functional connectivity observed between the amygdala and inferior frontal gyrus (in PHM+ vs. PHM-) during the angry task, indicates that PHM+ youth might be recruiting alternative structures for regulating emotion. This work sheds light on possible neural mechanisms by which genetic risk leads to the development of bipolar disorder.

Keywords: neuroimaging; implicit emotional processing; bipolar disorder; family history; child psychiatry

Disclosure: D. Hafeman, Nothing to Disclose; G. Bebko, Nothing to Disclose; M. Bertocci, Nothing to Disclose; H. Chase, Nothing to Disclose; S. Perlman, Nothing to Disclose; A. Hinze, Nothing to Disclose; M. Gill, Nothing to Disclose; C. Demeter, Nothing to Disclose; V. Diwadkar, Nothing to Disclose; J. Sunshine, Nothing to Disclose; D. Axelson, Nothing to Disclose; B. Birmaher, Nothing to Disclose; R. Kowatch, Nothing to Disclose; R. Findling, **Part 1:** Alexza, American Psychiatric Publishing, Bristol Myers Squibb, Dainippon Sumitomo Pharma, Forest, GlaxoSmithKline, Guilford Press, Johns Hopkins U Press, Kempharm, Lilly, Lundbeck, Merck, NIH, Novartis, Noven, Otuska, Pfizer, Physicians Postgraduate Press, Roche, Sage, Schering Plough, Seaside Therapeutics, Sepracor, Shire, Stanley Medical Research Institute, Sunovion, Supernus, Transcept, WebMD, **Part 2:** Guilford Press; Shire; WebMD, **Part 4:** Alexza Pharmaceuticals; Bristol-Myers Squibb; Forest Laboratories, Inc.; GlaxoSmithKline; Jo Merck & Co., Inc.; Novartis Pharmaceutical Corporation; Otsuka America Pharmaceuticals, Inc.; Pfizer Inc.; Schering-Plough; Shire Pharamceuticals Inc.; Stanley Medical Research Institute; Supernus Pharmaceuticals, Inc; M. Phillips, Nothing to Disclose.

T113. Emotional Face Encoding in Youth at Risk for Bipolar Disorder: A Preliminary fMRI Study

Melissa A. Brotman*, Brian L. Bones, Aviva K. Olsavsky, Nancy E. Adleman, Christen M. Deveney, Daniel P. Dickstein, Daniel S. Pine, Ellen Leibenluft

National Institute of Mental Health, Bethesda, Maryland

Background: Face memory has been proposed as a candidate endophenotype for bipolar disorder (BD) (Glahn et al 2010). However, researchers have yet to examine the neural correlates mediating face memory and encoding in youth. Both euthymic BD youth and children at familial risk show deficits in face emotion labeling (Brotman et al 2008), and demonstrate amygdala/parahippocampal gyrus hyperactivation during face processing (Olsavsky et al 2012). Pediatric BD patients and youth at-risk also show deficits in cognitive control (Brotman et al 2009), and prefrontal dysfunction during cognitive flexibility tasks (Kim et al 2012). Here, we compare neural activation during emotional face encoding in pediatric BD patients, children at familial risk with a first-degree BD relative, and healthy comparison youth. Behaviorally, we expect that pediatric BD patients and at risk youth will demonstrate deficits in face memory (Glahn et al 2010) and increased intrasubject variability in response time (ISV-RT) (Brotman et al 2009). During successful and unsuccessful encoding of faces, we hypothesize that both BD and at risk youth will demonstrate similar dysfunction in parahippocampal (Olsavsky et al 2012) and prefrontal (Kim et al 2012) regions mediating face emotion processing.

Methods: Functional magnetic resonance imaging (fMRI) data were acquired from 77 participants (8-18 years old), including 27 pediatric BD patients, 13 unaffected children at familial risk, and 37 healthy comparison youth. During the encoding phase of the study, fMRI data were acquired while subjects viewed a series of emotional faces in an event-related design. During separate blocks, subjects engaged in an explicit (rating hostility, subjective fear) or implicit (nose width or passive viewing) face viewing task. Using a subsequent-memory paradigm (Dickstein et al 2007), memory for faces was tested in a surprise recognition test outside the scanner. The memory test consisted of viewing neutral faces that included both previously-viewed actors who had displayed emotions in-scanner and novel actors. A d' score was calculated to measure performance during the post-scan memory task; higher d' indicates better performance and memory discrimination. The main contrast of interest was activation during the two implicit processing tasks (nose width or passive viewing) while viewing faces remembered accurately (hit) vs. not (miss). We conducted two whole-brain ANOVAs, one for each implicit encoding task, using a $p < 0.005$ threshold with clusters $\geqslant 45$ voxels.

Results: Groups did not differ on age, IQ, or sex distribution. There were no between group differences in face memory as measured by d'. However, consistent with our hypothesis, behavioral analyses revealed that BD ($p < .05$) and at risk ($p < .005$) youth demonstrated deficits in attention as measured by higher ISV-RT relative to healthy comparison youth during face encoding ratings (hostility, subjective fear, nose width). Groups did not differ in reaction time or face ratings. Whole-brain ANOVAs on the hit vs. miss contrast revealed two patterns of activity, with BD and at risk youth differing from healthy comparison youth. During the nose width encoding task, BD ($ps < .05$) and at risk

($ps < .005$) youth demonstrated left superior temporal gyrus and left parahippocampal gyrus hyperactivity relative to healthy comparison youth. However, during the passive viewing encoding task, BD ($ps < .005$) and at risk ($p < .05$; $p = .10$) demonstrated hypoactivity in the right middle temporal gyrus and inferior frontal gyrus.

Conclusions: While memory for faces has been proposed as a potential behavioral BD endophenotype (Glahn et al 2010), this is the first study to examine the neural correlates of this deficit in youth. Unexpectedly, groups did not differ behaviorally in face memory discrimination. However, consistent with prior work, relative to healthy comparison youth, BD and at risk children demonstrated behavioral deficits in attention, manifest as higher ISV-RT. BD and at risk youth also showed similar patterns of neural dysfunction. Together, these findings suggests that when BD and at risk youth are able to successfully remember faces, the attentional and neural mechanisms mediating encoding differ from healthy comparison youth. Specifically, we observed hyperactivation in parahippocampal and superior temporal regions, and hypoactivation in middle temporal and inferior frontal areas. Dysfunction in the parahippocampal gyrus and prefrontal cortex is consistent with prior work in at risk and BD youth (Kim et al 2012; Olsavsky et al 2012). The superior temporal area is involved in face and emotion perception (Said et al 2010), and is associated with the pathophysiology of pediatric BD (Pavuluri et al 2010). Our results build on work identifying behavioral deficits in face memory (Glahn et al 2010) by suggesting neural deficits associated with emotional face encoding. Future studies should include larger samples and a longitudinal design to determine whether the neural deficits associated with emotional face encoding predict the onset of BD in youth at risk for the illness. With further study, risk stratification and preventive interventions could be used to potentially mitigate the development and prevalence of BD.

Keywords: fMRI, bipolar disorder, youth at familial risk, face emotion, memory

Disclosure: M. Brotman, Nothing to Disclose; B. Bones, Nothing to Disclose; A. Olsavsky, **Part 4:** Dr. Olsavsky's research was made possible through the Clinical Research Training Program, a public-private partnership supported jointly by the NIH and Pfizer Inc. (via a grant to the Foundation for NIH from Pfizer Inc.); N. Adleman, Nothing to Disclose; C. Deveney, Nothing to Disclose; D. Dickstein, Nothing to Disclose; D. Pine, Nothing to Disclose; E. Leibenluft, Nothing to Disclose.

T114. Multivariate Analysis of Neural Activity Patterns Measured by Functional MRI Reveals Distinct Signatures of Antipsychotic Drug Action

Thomas Mueggler*, Celine Risterucci, Andreas Bruns, Basil Kuennecke, Edilio Borroni, Emilio Merlo Pich, Jean-Luc Moreau, Wettstein G. Joseph, Markus von Kienlin

F. Hoffmann-La Roche AG, Basel, Switzerland

Background: Pharmacological magnetic resonance imaging (phMRI) allows non-invasive assessment of drug effects in distinct brain regions providing functional information and revealing the neurocircuitry involved. Pharmacological MRI is increasingly utilized in drug discovery and development with the goal to expedite the translation of novel therapeutics and biomarkers from the laboratory to the clinic. Unlike the most commonly used blood-oxygenation-level-dependent (BOLD) contrast, the imaging modality of arterial spin labeling (ASL) provides absolute quantification of cerebral blood perfusion as a proxy of regional neuronal activity allowing direct comparisons between individuals. It also yields highly reproducible results over extended time intervals allowing direct within-subject comparisons. These characteristics make ASL-perfusion an ideal tool for phMRI to quantitatively elucidate drug effects on brain function in rodents. We applied ASL imaging to assess region-specific alteration of neural activity upon acute intervention with marketed typical and atypical antipsychotics and compared the response patterns with those elicited by well-described psychostimulants, aiming to identify a reference framework ultimately allowing profiling novel drug candidates for the treatment of schizophrenia.

Methods: Studies were conducted in anesthetized Sprague-Dawley rats on Bruker MRI instruments with a birdcage transmit coil and an actively decoupled surface receive coil. Images were acquired using continuous ASL (CASL) with a single-slice RARE readout module. Eight perfusion image planes were acquired within a period of 12 min. For subsequent registration to an anatomical template with an associated atlas defining 20+ regions of interest (ROIs), T2-weighted structural images were also acquired. Perfusion values for each ROI were normalized to brain-mean perfusion to derive region-specific values independent of inter-individual differences of the animals' global hemodynamic status. The study design comprised one or more doses of six marketed antipsychotics and two psychomimetics ($n \geqslant 8$ per condition). ROI-wise differences vs. control (vehicle) were tested for significant regional drug effects using univariate statistics, and were also subjected to a principal component analysis (PCA) to extract multiple-ROI activation patterns characterizing the drug responses.

Results: Acute dosing with the antipsychotics led to distinct, region-specific and reproducible changes in normalized perfusion as compared to vehicle treatment in brain regions implicated in schizophrenia such as the medial prefrontal cortex, temporal cortex, entorhinal (piriform) cortex, nucleus accumbens, ventral tegmental area and substantia nigra. The multiple-ROI response patterns were highly similar among the different antipsychotics assessed and were clearly separable from responses to the psychostimulants, even revealing opposing effects in key brain areas. Both classes, in turn, deviated from patterns observed after acute dosing with different classes of drug such as tricyclic antidepressants (e.g., desipramine).

Conclusions: We have identified ASL-based perfusion patterns of antipsychotic and psychomimetic drug action comprising key neuroanatomical substrates underlying the symptomatology in schizophrenia. Such drug signatures can provide a framework for assessing similarities and means for differentiating domains-of-action, dose-effects relations, the link between treatment duration and effects of novel antipsychotic compounds, and to identify imaging biomarkers. Although ASL-based phMRI studies in humans are still sparse, recent progress in commercialization is expected to foster translation of ASL into clinical trials.

Keywords: imaging, functional MRI, antipsychotic, schizophrenia, biomarker

Disclosure: T. Mueggler, **Part 4:** Emloyment with F. Hoffmann-La Roche, Switzerland; C. Risterucci, **Part 4:** Employment with Hoffmann-La Roche Ltd, Switzerland; A. Bruns, **Part 4:** Employment with Hoffmann-La Roche Ltd, Switzerland; B. Kuennecke, **Part 4:** Employment with Hoffmann-La Roche Ltd, Switzerland; E. Borroni, **Part 4:** Employment with Hoffmann-La Roche Ltd, Switzerland; E. Merlo Pich, **Part 4:** EMP declares that during the past three year he was full-time employee of GlaxoSmithKline in 2010-11 and since 2012 he has been a full-time employee of F. Hoffmann-La Roche, Basel; J. Moreau, **Part 4:** Employment with Hoffmann-La Roche Ltd, Switzerland; W. Joseph, **Part 4:** Employment with Hoffmann-La Roche Ltd, Switzerland; M. von Kienlin, **Part 4:** Employment with Hoffmann-La Roche Ltd, Switzerland.

T115. Network-level Disruptions in Intrinsic Functional Connectivity across Psychotic Disorders

Justin T. Baker*, Avram J. Holmes, Randy L. Buckner, Dost Ongur

McLean Hospital/Harvard Medical School, Belmont, Massachusetts

Background: Psychotic disorders (including schizophrenia, schizaffective disorder, and psychotic bipolar disorder) are devastating illnesses with tremendous social costs but unknown pathophysiology. They are characterized by breakdown in the integration of cortical information processing. Recent advances in neuroimaging data methods have allowed for the estimation of brain regions and

networks on the basis of intrinsic functional connectivity (e.g., Smith et al., Yeo et al. 2011), but the specific network abnormalities in psychotic disorders are poorly understood.
Methods: Here we compare intrinsic functional connectivity across the cerebral cortex in a cohort of 100 patients with schizophrenia or psychotic bipolar disorder and 100 healthy control subjects, using network-level analyses of resting state functional magnetic resonance imaging (rs-fMRI) data. Patients with psychotic bipolar disorder (n = 49), schizophrenia (n = 23), or schizoaffective disorder (n = 28) and control participants (n = 100; matched for age, gender, race, handedness, and scan quality) underwent brief fMRI runs, while instructed to keep still with their eyes open. Analyses were designed to identify differences between patients and controls in the BOLD rs-fMRI functional connectivity profiles across the cerebral cortex without imposing prior assumptions about the location of effects.
Results: Relative to healthy participants, individuals with a psychotic illness had significant and selective reductions in functional connectivity between a set of cortical regions belonging to the frontoparietal control network ($p < 0.05$, FWE-corrected). This functionally defined network is comprised of dorsolateral prefrontal cortex, posteromedial prefrontal cortex, lateral parietal cortex, and posterior temporal cortex. The effect was shared across diagnostic entities and persisted after matching patients and controls on the basis of head motion. Abnormalities in other brain networks were present, although less pronounced, failing to survive our FWE statistical criterion.
Conclusions: The frontoparietal control network is preferentially disrupted in individuals with a psychotic illness. Given this network's putative role in flexible guidance of cognition, this disruption may underlie the shared vulnerability to thought disorder that characterizes both schizophrenia and affective psychosis. This finding highlights the utility of transdiagnostic approaches to studies of mental illness etiology that seek to establish correspondances between symptom domains and network-level disruptions in brain connectivity.
Keywords: functional connectivity, connectomics, psychosis, schizophrenia, bipolar disorder
Disclosure: J. Baker, Nothing to Disclose; A. Holmes, Nothing to Disclose; R. Buckner, Nothing to Disclose; D. Ongur, Nothing to Disclose.

T116. Brain Response to Stress and to Smoking Cues Predicts Relapse to Tobacco Smoking

Christian G. Schütz*, Martin Landsberg, Marcel Daamen, Gisela Bopp, Lukas Scheef

UBC, Vancouver, Canada

Background: Several fMRI studies on tobacco dependence and as on other substances have identified the specific importance of the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), and the amygdala in drug-related cue reactivity. Recently the corticostriatal-limbic activation involving the hippocampus, insula, and anterior and posterior cingulate have been implicated in stress induced brain reactivity. Assuming a connection between baseline response to cues and stress and relapse, the aim of this study was to determine whether the reactivity at baseline predicts outcome of nicotine cessation treatment after six months.
Methods: 18 smokers consuming at least 15 cigarettes a day for more than two years and 15 controls were included in a cue-reactivity paradigm consisting of six video sequences with smoking-related cues and six video sequences with neutral nature scenes, as well as six stress tasks based on the Trier Stress Test (calculating under social stress) and six controls (counting). All participants in the study had agreed beforehand to take part in a six months nicotine dependence treatment program. Relapse was assessed regularly and objectively with CO measurements over a six-month period. Of the 18 smokers, nine (age: 38.9 +/− 6.9 yrs; 5 male, 4 female) relapsed during the treatment program ("relapse group"), while nine (age: 40.3 +/− 7.4 yrs; 3 male, 6 female) remained abstinent ("abstinence group"). The fMRI-examinations were performed on an Achieva 3.0T whole body MRI system (Philips, Best, Netherlands). Further technical details were as follows: Birdcage quadrature headcoil, GE-Single Shot EPI (TE/TR/Flip = 35/3000/90°), 3.6x3.6x3.6 mm3, 3 runs with each 245 dynamic scans. Preprocessing and statistical analyses were conducted with SPM2. Brain activation of relapsed smokers and abstinent smokers was compared by calculating the contrast cue videos minus neutral videos, and as the contrast stress task minus non-stress task.
Results: Both cues and stress induced craving in smokers. Brain reactivity differed in smokers and controls, as well as in low and high cravers. Craving though did not predict relapse. A total of 9 out of 18 smokers relapsed within six months. The categorical comparison revealed enhanced activity in the "relapse group" in the DLPFC (bilateral), OFC (bilateral), ACC, supplemental motor area and parietal cortex ($p < 0.005$, uncorrected), when comparing the cue versus the control videos. In the stress induced reactivity bilateral activation of the insula ($p < 0.01$) was associated with an increased risk to relapse in 6 months.
Conclusions: Consistent with our hypothesis, we were able to show that brain regions associated with nicotine craving were differentially more activated in smokers who relapsed during the cessation treatment compared to smokers that remained abstinent. These findings support the role of frontal and anterior cingulate region in cue responsivity. Brain regions predicting relapse can be related to attentional and intentional processes. Our findings are consistent with an increased incentive value of tobacco predicting relapse. The role of the insula in smoking relapse has received recent attention playing a major role in mediating craving, as well as decision-making. While our result is consistent with previous findings, it remains to be determined why the insula is the only brain region predicting relapse within the mild social stress paradigm. Determining the role of specific brain regions in conscious versus non-conscious response might be a next step in understanding the relationship of craving and relapse. Overall, these data support previous findings indicating that brain activity levels in specific brain regions may serve as a predictor for treatment outcome.
Keywords: tobacco, fmri, cue, stress, relapse
Disclosure: C. Schütz, Nothing to Disclose; M. Landsberg, Nothing to Disclose; M. Daamen, Nothing to Disclose; G. Bopp, Nothing to Disclose; L. Scheef, Nothing to Disclose.

T117. Greater Activation in the Anterior Cingulate Cortex is Related to Less Social Anxiety in Young Adults at Temperament-based Risk

Jacqueline A. Clauss*, Suzanne Avery, Ross VanDerKlok, Jennifer Urbano. Blackford

Vanderbilt University School of Medicine, Nashville, Tennessee

Background: Inhibited temperament is the tendency to respond to novel situations or people with wariness or avoidance behaviors. Inhibited temperament is biologically-based, heritable, and present in about 15% of infants at birth. Throughout the lifetime, inhibited temperament remains relatively stable, and is associated with a 7-fold increased risk for developing social anxiety disorder. A key component of both inhibited temperament and social anxiety disorder is anticipatory anxiety, especially prior to social situations. Anticipatory anxiety is characterized by intense distress, physiological arousal (e.g., nausea, sweating, and heart racing), and avoidance behaviors. To understand the neural processes underlying anticipatory anxiety in inhibited temperament, we used functional MRI (fMRI) to examine brain activation while subjects were anticipating negative social stimuli (fear faces).
Methods: Thirty-four young adults with either inhibited (n = 17) or uninhibited (n = 17) temperament participated in the study. Temperament was assessed using current and retrospective self-report measures; social anxiety symptoms were measured using the Social Phobia and Anxiety Inventory. FMRI was used to measure brain activation during anticipatory processing. The fMRI task included a training phase and a test phase. During the training

phase, subjects were trained on the association between a specific cue and a fear face, and another cue and a neutral face. During the test phase, subjects were presented with 80 trials (40 fear, 40 neutral) consisting of: a cue; a brief anticipation period (5-9 seconds); and a fear or a neutral face. Group differences in anticipatory processing (fear > neutral) were assessed using a two-sample *t*-test. To examine the relationship between anticipatory brain response and social anxiety symptoms, a regression analysis was performed within the inhibited temperament group. To identify temperament differences in patterns of connectivity, a functional connectivity analysis was performed. Cluster-based thresholds were used to control for Type I error (family-wise corrected, $p < .05$) in all analyses.

Results: During anticipation, inhibited individuals had significantly greater activation, relative to uninhibited individuals, in three regions of the prefrontal cortex ($p^* < .05$, corrected): rostral anterior cingulate cortex; dorsal anterior cingulate cortex; and bilateral dorsolateral prefrontal cortex. Amygdala activation during anticipation was similar between the two groups, and there were no brain regions where activation was greater in the uninhibited group. Within the inhibited group, social anxiety symptoms correlated with activation; individuals with greater activation in both the rostral and dorsal anterior cingulate cortices had fewer social anxiety symptoms ($p^* < .05$, corrected). Finally, connectivity analyses using a rostral anterior cingulate seed region revealed temperament differences in connectivity with the amygdala ($p^* < .05$, corrected), characterized by negative connectivity in the inhibited group and modest positive connectivity in the uninhibited group.

Conclusions: During a social anticipation task, inhibited individuals displayed prefrontal cortical activation that was absent in uninhibited individuals, suggesting that inhibited individuals actively prepared for viewing the upcoming fear face. The prefrontal regions engaged during this task are similar to regions engaged by healthy controls during anticipation of highly aversive stimuli and by patients with an anxiety disorder during anticipation of phobic stimuli. Importantly, degree of prefrontal activation was associated with fewer social anxiety symptoms, indicating that activation of these regions in inhibited individuals likely reflected adaptive processes. Supporting this view rostral anterior cingulate cortex in the inhibited group was negatively correlated with amygdala activation, which may reflect suppression of amygdala reactivity by prefrontal regions. In conclusion, the results of this study suggest that individuals with an inhibited temperament engage prefrontal cortex regulatory regions during anticipation of viewing mildly aversive social stimuli and that greater activation of these regions is adaptive. Treatments that strengthen anterior cingulate cortex activation may be effective in preventing the development of social anxiety disorder in at-risk individuals.

Keywords: inhibited temperament, social anxiety, fMRI, anticipation, fear faces, anterior cingulate

Disclosure: J. Clauss, Nothing to Disclose; S. Avery, Nothing to Disclose; R. VanDerKlok, Nothing to Disclose; J. Blackford, Nothing to Disclose.

T118. Neuroanatomical Correlates of Altered Immune Function in Late-life Depression

Olusola Ajilore*, Ghanshyam N. Pandey, Rebecca Charlton, Laura Korthauer, Melissa Lamar, Shaolin Yang, Xinguo Ren, Anand Kumar

University of Illinois at Chicago, Chicago, Illinois

Background: Elevations in pro-inflammatory cytokines have been implicated in the pathophysiology of major depression. However, the relationship between elevated pro-inflammatory cytokines and structural abnormalities associated with depression is not well characterized. The purpose of this study was to examine the neuroanatomical correlates of elevated IL-6, TNF-a, and IL-1b in late-life depression (LLD).

Methods: We recruited 22 subjects with late-life major depression (LLD) and 21 healthy comparison subjects (HC) from the community. All subjects were 60 years of age or older. Serum levels of IL-6, TNF-a, and IL-1b were assayed. Subjects were scanned on a 3T Phillips Achieva MRI scanner. White matter hyperintensities (WMH) were measured using a semi-automated technique. Anterior cingulate cortex (ACC) thickness and hippocampal volumes were measured using Freesurfer.

Results: IL-6, TNF-a, and IL-1b were elevated in LLD subjects but only increases in IL-6 reached statistical significance. IL-6 was significantly associated with Geriatric Depression Scale scores in LLD subjects ($r = .524$, $p = .012$). In HC subjects, IL-6 and IL-1b were negatively correlated with hippocampal volume (IL-6: $r = -.72$, $p = .002$; IL-1b: $r = -.493$, $p = .037$) and positively correlated with WMH (IL-6: $r = .631$, $p = 01$; IL-1b: $r = .55$, $p = .026$). In both HC and LLD subjects, TNF-a was positively correlated with ACC thickness (HC: $r = .58$, $p = .015$; LLD: $r = .542$, $p = .028$).

Conclusions: Elevations in pro-inflammatory cytokines are significantly associated with structural alterations in brain regions thought to play a role in the pathophysiology of major depression.

Keywords: geriatric depression, cytokines, neuroimaging, neuroinflammation

Disclosure: O. Ajilore, Nothing to Disclose; G. Pandey, Nothing to Disclose; R. Charlton, Nothing to Disclose; L. Korthauer, Nothing to Disclose; M. Lamar, Nothing to Disclose; S. Yang, Nothing to Disclose; X. Ren, Nothing to Disclose; A. Kumar, Nothing to Disclose.

T119. Naltrexone Modulates Anticipatory Responses to Reward

Tiffany Love*, Chelsea Cummiford, Brian J. Mickey, Joseph Heffernan, Evan Chang, Jon-Kar Zubieta

University of Michigan, Ann Arbor, Michigan

Background: The endogenous opioid system plays a key role in the processing of reward-related stimuli. Animal models have demonstrated that opioid receptors are recruited in response to rewarding stimuli, such as food or drugs of abuse, and treatment with opioid antagonists, like naltrexone (NTX), can reduce the positive reinforcing properties of such rewards. As such, NTX and other opioid antagonists and partial agonists are often prescribed for the treatment of substance dependence (particularly alcohol dependence) to lower the reinforcing effects of drugs and to curb compulsive drug taking. However, the effects of NTX on reward networks in humans remain poorly understood. We sought to determine whether brain activity observed during the performance of a monetary incentive delay task was affected by NTX treatment.

Methods: Eight healthy male participants were recruited via advertisement. Blood oxygenation level dependent (BOLD) responses were quantified using functional magnetic resonance imaging during a monetary incentive delay task, which is specifically designed to examine the neural circuitry responsive to the anticipation of rewards. Participants were scanned (1) at baseline, (2) following 7 days of NTX treatment (50 mg/day), (3) 1 day after discontinuation of NTX, and (4) 2 days after discontinuation of NTX. Data was subjected to analysis with a repeated-measures general linear model using SPM8.

Results: During the anticipation of reward, paired *t*-tests revealed significantly greater BOLD activity within the right anterior insula ($t = 8.22$, $p_{FWE-cluster} = 0.010$, $k = 663$) at baseline compared to activity following 7 days of NTX treatment. Functional data from this region was extracted, percent signal change was calculated, and additional analyses were performed in SPSS. Repeated measures analyses revealed that 1 day after discontinuation of NTX, activity within this region was no longer statistically different from baseline activity ($F = 4.25$, $p = 0.017$; pairwise comparisons with Bonferroni adjustment for multiple comparisons: Baseline > 7 days NTX treatment, $p = 0.024$; Baseline > 1 day post treatment, $p > .99$; Baseline > 2 days post treatment, $p > .99$).

Conclusions: We found significant attenuation of BOLD activity within the anterior insula during the anticipation of reward following one week

of NTX treatment in healthy males. The anterior insula is rich in mu opioid receptors and is recruited during reward processing, so the effects of NTX that we observed could be a direct local effect of occupancy of mu opioid receptors. Interestingly, one day after discontinuing treatment, activity within this region returned to baseline levels. In the context of treatment of substance use disorders where treatment compliance is a concern, our results suggest that regional brain effects of NTX on the processing of rewards may be vulnerable to even brief interruptions in NTX treatment. Funding agency: Work supported by grant R01 DA027494-01-S1 from the National Institute of Drug Abuse
Keywords: naltrexone, fmri, reward
Disclosure: T. Love, Nothing to Disclose; C. Cummiford, Nothing to Disclose; B. Mickey, **Part 4:** Dr. Mickey has received salary support from St. Jude Medical for unrelated research; J. Heffernan, Nothing to Disclose; E. Chang, Nothing to Disclose; J. Zubieta, **Part 1:** Dr. Zubieta has served as a paid consultant for Eli Lilly and Co., Johnson & Johnson, Merck, and Abbott

T120. Genetic Studies of PTSD in Ohio National Guard Soldiers Deployed to Iraq and Afghanistan: Replication of G x E Interaction in FKBP5 and 5-HTTLPR

Anthony P. King*, Peng Zhang, Sebastian Zoellner, Michael Camilleri, Sandro Galea, Marijo Tamburrino, Joseph R. Calabrese, Israel Liberzon

University of Michigan Medical School, Ann Arbor, Michigan

Background: Posttraumatic stress disorder (PTSD) is a chronic, debilitating disease that leads to substantial human suffering and costs to society. Military deployment and exposures to combat trauma are associated with high incidence of PTSD, estimates of up to 1 in 5 US soldiers and Marines deployed to Iraq developed clinically significant symptoms of PTSD. Twin and family studies suggest that PTSD is heritable, with estimates of up to 40% of variance in PTSD symptoms explained by genetic factors. Molecular genetic studies of candidate genes in trauma-exposed populations has not found "main effects" of gene association with PTSD, but rather have suggested gene x environment (G x E) interaction, (including gene x childhood adversity interactions), in the serotonin transporter (*SLC6A4*), *FKBP5* and *RGS2* genes, but these have not been replicated.
Methods: A random sample of 2616 Ohio Army National Guard (ONG) soldiers was recruited, and structured telephone interviews were conducted at three time points (pre- and post-deployment, "Waves" 1-3) to assess deployment-related and lifetime traumatic event exposure, including childhood abuse and adversity, and DSM-IV criteria PTSD (interview adapted from PTSD Checklist, PCL). Deployments included Afghanistan (OEF), Iraq (OIF), and other operations. Additional psychiatric symptoms were obtained using validated instruments, and other data using multi-measure scales adapted from the Deployment Risk and Resilience Survey. Soldiers were requested on Wave 2 interview to consent to provide saliva specimens and additional self-report measures, collection kits (Oragene) were sent to participant's homes and shipped to our lab by return mail. Genomic DNA was purified using a semi-automated filter-based system. Genotyping was performed using PCR (serotonin transporter gene (*SLC6A4*) 5-HTTLPR, *DRD4* VNTR), and a custom 4800 SNP Illumina array. This array maps ~120 candidate genes and genomic regions previously identified in candidate or GWAS studies of other psychiatric disorders, and includes *FKBP5*, *RGS2*, and *CRHR1* genes previously implicated in PTSD, as well as ancestry informative markers. Standard Illumina clustering and data cleaning was performed, data pruning generated 1500 markers in equilibrium for principal component analyses to control for population substructure. Association of previously reported variants with level of PTSD symptoms was tested in GLM modeling of main effects of gene (SNP), controlling for levels of childhood abuse (0, 1, or 2 or more types), and lifetime trauma load (ordinal 1-4 levels), and also including gene x child abuse and gene x trauma load interaction terms.
Results: The majority of soldiers (80%) agreed to be sent a genetic specimen collection kit, and 1042 returned genetic specimens and self-report data (50% return rate). 136 participants did not endorse any lifetime trauma, and were excluded from further analyses. The highest of the available PCL scores was used for association analyses (available data $N = 766$). As expected, PCL score was associated with report of child abuse ($F[2,754] = 12.4$. $p < .00001$) and lifetime trauma load ($F[3,753] = 14.9$. $p < .00001$). Four SNPs in *FKBP5* (rs1360780, rs3800373, rs9296158, rs9470080) all showed SNP x child abuse interactions (all $p < .007$), but no main effect on PCL. The triallelic 5-HTTLPR also showed gene x child abuse interaction in a recessive model ($p < .005$), but no main effects. *RGS2*, *DRD4*, and *CRHR1* all showed no main effects and no interaction effects for association with PCL.
Conclusions: To our knowledge, this is the first report of genetic association with PTSD symptoms in soldiers deployed to Iraq and Afghanistan. We have replicated previous findings of G x E interaction effects in *FKBP5* and 5-HTTLPR in this cohort. Further analyses are ongoing to identify additional genetic variants associated with PTSD.
Keywords: PTSD, genetics, gene x environment interaction, military, combat trauma
Disclosure: A. King, Nothing to Disclose; P. Zhang, Nothing to Disclose; S. Zoellner, Nothing to Disclose; M. Camilleri, Nothing to Disclose; S. Galea, Nothing to Disclose; M. Tamburrino, **Part 4:** I have 20% of my university salary paid through a Dept. of Defense Congressionally Directed Medical Research Program : W81XHW-07-1-0409, the "Ohio Army National Guard Mental Health Initiative"; J. Calabrese, **Part 1:** Research from AHRQ, California Bipolar Foundation, Cephalon, Department of Defense, NIMH, Stanley, Sunovion., Consulted to or served on advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo, EPI-Q, Inc., Forest, France Foundation, Glaxo Smith Kline, Janssen, Johnson and Johnson, Lundbeck, Merck, Neurosearch, Ortho McNeil, Otsuka, Pfizer, Repligen, Schering-Plough, Servier, Solvay, Supernus, Synosia, Takeda, and Wyeth, CME lectures supported by AstraZeneca, Bristol-Myers Squibb, France Foundation, Glaxo Smith Kline, Janssen, Johnson and Johnson, Merck, Sanofi Aventis, Schering-Plough, Pfizer, Solvay, and Wyeth, No speaker bureaus nor stock, equity, nor patents, **Part 2:** AstraZeneca, Lundbeck, Merck, **Part 3:** AstraZeneca, **Part 4:** AHRQ, California Bipolar Foundation, Cephalon, Department of Defense, NIMH, Stanley, Sunovion; I. Liberzon, Nothing to Disclose.

T121. Auditory Steady State Response and Auditory Cortex Volume Deficits in Schizophrenia

Yoji Hirano*, Naoya Oribe, Robert W. McCarley, Kevin M. Spencer

VA Boston Healthcare System / Harvard Medical School, Boston, Massachusetts

Background: Disruption in the oscillatory activity of neural circuits have been suggested to play a critical role in the pathophysiology of schizophrenia which may lead to positive symptoms such as hallucinations or delusions. Forty Hz auditory steady state response (ASSR) impairments have been reported and hypothesized to reflect these neural network abnormalities in the primary auditory cortex of chronic and first episode schizophrenia patients (SZ) compared to healthy controls (HC). Structural magnetic resonance imaging (MRI) studies have reported reductions in the volume of auditory cortex in SZ, and furthermore, post-onset progressive volume reductions of auditory cortex were found in first episode SZ. However, the relationship between gamma ASSR deficits and structural abnormalities of the auditory cortex in schizophrenia is not clear. Here we examined whether 40 Hz ASSR deficits in SZ are associated with volume reductions of primary auditory cortex (Heschl's gyrus; HG), particularly in the left hemisphere, where both abnormalities have been associated with auditory hallucinations.

Methods: The electroencephalogram (EEG) was recorded from 24 SZ (4 females) and 24 HC (4 females) matched for age, handedness, and premorbid intelligence. Stimuli were 20-, 30-, and 40-Hz binaural click trains. Time-frequency analyses (PLF: phase locking factor, evoked power) were computed with the Morlet wavelet transform on scalp electrode and source data. ASSR sources were localized with a 4-dipole model consisting of tangential and radial dipoles in the auditory cortex in each hemisphere. Structural MR images were acquired in 23/24 SZ and in 24/24 HC using a 3-Tesla GE Echospeed system. MRI volumes were calculated for gray matter of auditory cortex including HG and planum temporale (PT) as regions of interest. Clinical symptoms were assessed by SAPS and SANS.
Results: PLF of the 40 Hz ASSR was reduced in SZ compared to HC at left temporal electrodes and left tangential and radial dipoles. There were no significant group differences in evoked power, nor in PLF or evoked power for the 20- and 30-Hz ASSRs. MRI results showed significant left lateralized volume reductions of HG and PT in SZ compared to HC. PLF of the 40 Hz ASSR at left hemisphere electrodes was correlated with left HG volume reduction in SZ, whereas no correlations were found between PLF and PT volumes. Moreover, PLF for both the left hemisphere tangential and radial dipoles was correlated with left HG gray matter volume in SZ. Left hemisphere electrode PLF was negatively correlated with total positive symptoms, and left radial dipole PLF was negatively correlated with duration of illness.
Conclusions: These findings provide the first link between gamma oscillation and gray matter deficits in schizophrenia, and strengthen the proposal that the 40 Hz ASSR is a sensitive measure of the integrity of primary auditory cortex circuitry. These results imply that reduced synaptic connectivity may be a cause of gamma deficits, in addition to reduced inhibitory neurotransmission, as suggested by a previous computational modeling study.
Keywords: Schizophrenia; Gamma oscillation; Auditory steady state response; Electroencephalogram; MRI; Heschl's gyrus
Disclosure: Y. Hirano, Nothing to Disclose; N. Oribe, Nothing to Disclose; R. McCarley, Nothing to Disclose; K. Spencer, **Part 1:** Galenea, Inc.: paid consultant. Bristol-Myers Squibb: paid consultant, **Part 4:** Research and Development Grant from Galenea, Inc.

T122. Transcriptional Profiling of Multiple Brain Regions from Matched Cohorts of Subjects with Schizophrenia, Bipolar Disorder, and Major Depressive Disorder

Thomas A. Lanz*, Simon Xi, Diogo M. Camacho, Susan E. Bove, Veronica Reinhart, Max Kuhn, Phillip Yates, Dmitri Volfson, David A. Lewis, Robin J. Kleiman, Nicholas Brandon

Pfizer, Cambridge, Massachusetts

Background: Schizophrenia is a complex psychiatric disorder encompassing a range of symptoms and etiology dependent upon the interaction of genetic and environmental factors. Several risk genes, such as DISC1, have been associated with schizophrenia as well as bipolar disorder (BPD) and major depressive disorder (MDD), consistent with the hypothesis that a shared genetic architecture could contribute to divergent clinical syndromes. The present study compared gene expression profiles across three brain regions in post-mortem tissue from matched subjects with schizophrenia, BPD or MDD and unaffected controls. Multiple analytical methods were applied to differentially expressed gene sets to gain a better understanding of individual genes, gene networks, and signaling pathways dysregulated in three functionally inter-connected regions: hippocampus, frontal cortex, and associative striatum. Genes previously implicated in conferring risk of psychiatric disease were also specifically evaluated.
Methods: Post-mortem brain tissue was collected from control subjects and well-matched subjects with schizophrenia, BPD, and MDD (n = 19 from each group). RNA was isolated from hippocampus, Brodmann Area 46, and associative striatum and hybridized to U133_Plus2 Affymetrix chips. Data were normalized by RMA, subjected to pairwise comparison followed by Benjamini and Hochberg False Discovery Rate correction (FDR). Pathway analysis was performed on differentially-expressed genes from each disease cohort compared to control, and results were compared with those obtained using gene-set enrichment analysis (GSEA). To examine changes in gene-gene relationships in the disease state, network inference was applied to the data and correlation networks were identified. Gene pairs which showed changes in correlation in the disease state were subjected to pathway analysis using Nextbio. The results of all three pathway approaches were compared, and the data were further interrogated to examine changes in gene with variants associated with schizophrenia.
Results: Samples derived from patients with schizophrenia exhibited many more changes in gene expression across all brain regions than observed in BPD or MDD. Several genes showed changes in both schizophrenia and BPD, though the magnitude of change was usually larger in schizophrenia. All methods of pathway analysis identified multiple common dysregulated pathways in more than one brain region from schizophrenia including PPAR signaling, ERK and CREB signaling pathways, notch signaling, insulin signaling, and a variety of metabolic and immunological pathways. Differential gene expression and analysis of changes in gene-gene correlations highlighted several risk genes for schizophrenia, including GWAS hits (TCF4 and NT5C2), genes highlighted in SzGene (e.g. RGS4 and AHI1), and multiple interacting partners of DISC1.
Conclusions: The present study examined changes in gene expression in samples collected across brain regions from a cohort of well-matched psychiatric patients. Based on gene expression, the post-mortem molecular pathology observed in schizophrenia was more severe than in bipolar disorder or major depressive disorder. The degree of overlap in both genes and pathways between brain regions suggests perturbation of common cellular processes across neural circuits. Several genes that have variants associated with schizophrenia were found to have altered expression in multiple regions of brains from subjects with schizophrenia. Continued evaluation of circuit-level alterations in gene expression and gene-network relationships may further our understanding of how genetic variants may be influencing biological processes to contribute to psychiatric disease.
Keywords: schizophrenia microarray post-mortem gene expression
Disclosure: T. Lanz, **Part 4:** Employee of Pfizer; S. Xi, **Part 4:** Employee of Pfizer; D. Camacho, **Part 4:** Employee of Pfizer; S. Bove, **Part 4:** Employee of Pfizer at the time these experiments were performed; V. Reinhart, **Part 4:** Employee of Pfizer; M. Kuhn, **Part 4:** Employee of Pfizer; P. Yates, **Part 4:** Employee of Pfizer; D. Volfson, **Part 4:** Employee of Pfizer; D. Lewis, Nothing to Disclose; R. Kleiman, **Part 4:** Employee of Pfizer at the time these experiments were performed; N. Brandon, **Part 4:** Employee of Pfizer at the time these experiments were performed.

T123. High Rate of Rare and of Disease Related Copy Number Variants in Childhood Onset Schizophrenia

Judith L. Rapoport*, Kwangmi Ahn, Nitin Gogtay, Peter Gochman, Tiffany Andersen

DIRP, NIMH, Bethesda, Maryland

Background: Childhood Onset Schizophrenia (COS)is a rare severe form of the disorder with more striking cognitive and neurobiological abnormalities. One rationale for the study was that very early onset patients across all of medicine, generally have more salient genetic risk.
Methods: Since 1990 we have screened nationally for non intellectually impaired COS cases and confirmed the diagnosis in 125 with inpatient observations . For 121 of these patients, and all available first degree relatives (115 full siblings and 192 parents) we obtained array based screening of DNA using the 1M illumina chip for most cases (and using imputed 2.5M illumina chip data for 5 probands and their families). The database of genetic variation

(DGV) was also referenced which currently totals over 326,000 individuals for whom hap map or array CNV data is available. Two types of CNVs were measured. We sought to compare rates of disease related CNVS (for schizophrenia, autism or cognitive impairment). A COS – healthy sib comparison was available for 66 COS patients for rates of total, disease related, and rare CNVs. In addition we sought CNVs >100 kb in size that interrupted a gene that had not been reported in the DGV even though not previously associated with illness.
Results: The COS patients had a significantly higher rate of disease related and rare CNVs by several measures. A total of 5 (4%) COS and no healthy siblings had a 2.4 MB hemideletion at 22q11. This is higher than the rate of 0.02% seen in healthy controls (P = .0001) and than the rate of 0,4% seen in adult onset patients (p = .001). After omitting the 5 22q11 patients, the 66 COS with a healthy full sibling were compared with data from that sibling with respect to rate of disease related CNVs. The COS had a higher rate than did their siblings (p = <.03). When rare non shared CNVs (not previously associated with disease, not in the DGV) were compared for the 66 COS-healthy sib pairs, the COS probands had significantly more private rare CNVs (p = .02).
Conclusions: Childhood Onset Schizophrenia patients have more salient genetic risk factors than do healthy siblings and the general public. For several measures, these rates are also higher than for adult onset patients (22q11, MYT1). Most striking are the higher rates of private non shared rare CNVs that deserve further study.
Keywords: schizophrenia, genetics, childhood onset, copy number variants, 22q11 deletion
Disclosure: J. Rapoport, Nothing to Disclose; K. Ahn, Nothing to Disclose; N. Gogtay, Nothing to Disclose; P. Gochman, Nothing to Disclose; T. Andersen, Nothing to Disclose.

T124. A Factor Analysis of GABAergic Gene Expression across 16 Brain Regions in Human Postmortem Samples Identifies Specificity in Response to Chronic Alcohol and Cocaine Exposure

Mary-Anne Enoch*, Basel Baghal, Qiaoping Yuan, David Goldman

National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, Maryland

Background: $GABA_A$ receptors are responsible for the fast synaptic transmission of GABA, the major inhibitory neurotransmitter in the CNS. $GABA_A$ receptors have been implicated in the acute and chronic effects of alcohol and also in anxiety. Genes encoding the majority of the 19 subunits comprising these pentameric receptors are clustered on chromosomes (chrs) 4, 5, 15 and X. A key question is whether the expression of genes within each chromosomal cluster are correlated (cic effects) and whether there is correlation of gene expression between GABAergic genes that are located in different regions (trans effects). The purpose of this study was to identify global patterns of GABAergic gene expression in healthy controls before considering the effects of chronic exposure to alcohol and cocaine.
Methods: We obtained RNA-Seq data from postmortem samples of 16 brain regions from nine healthy men and women aged 18 – 40 who died suddenly. The RNA-Seq data was obtained from BrainSpan, a publicly available resource (http://www.brainspan.org/). In addition to the $GABA_A$ subunit genes we included genes encoding the two $GABA_B$ receptor subunits (*GABBR1, GABBR2*), genes encoding proteins involved in GABA synthesis (*GAD1*, *GAD2*) and GABA regulation (*GPHN*, *SLC6A1* and *PRAF2*). A factor analysis was performed to identify patterns of cis and trans correlations in gene expression. In order to determine whether there was specificity of factor response to the effects of chronic alcohol or cocaine exposure we looked at gene expression data from an earlier RNA-Seq study in which we had identified changes in GABAergic gene expression in human postmortem samples of hippocampus from alcoholics, cocaine addicts and controls (Zhou et al, PNAS 2011; Enoch et al, PLoS ONE 2012).
Results: Six factors were identified that together accounted for 0.86 of the total variance in GABAergic gene expression. Most genes loaded onto only one factor; 6 genes loaded onto 2 factors. Results are presented for the main factor loading for each gene. Factor 1 (0.30 variance) included genes encoding seven $GABA_A$ subunits and the $GABA_BR2$ subunit. The strongest loading (0.9) was for the chr 5 cluster of genes that together encode the most abundant $GABA_A$ receptor subunit group: $alpha_1beta_2gamma_2$. Two chr 15 genes: *GABRB3* and *GABRG3* also had high loadings (0.8). Five genes loaded onto factor 2 (0.17 variance) all of which are implicated in GABA transport across the synaptic cleft: *SLC6A1, GABBR1*, *PRAF2*, *GPHN* and *GAD1*. Loading onto factor 3 were three chr 4 genes (0.14 variance) that encode the $GABA_A$ subunit combination $alpha_2beta_1gamma_1$ found almost exclusively in the mesolimbic reward pathway. There were two cerebellar factors: factor 4 (0.10 variance) included two low expression genes, *GABRA5* and *GABRQ* and factor 5 (0.09 variance) included two highly expressed genes, *GABRA6* and *GABRD* that encode two extrasynaptic $GABA_A$ subunits. Finally only *GAD2* loaded onto factor 6 (0.06 variance). Further analyses showed that the genes loading onto factor 2 (synaptic transport), factor 3 (chr4 gene cluster), factor 5 (high cerebellar expression,) and factor 6 (*GAD2* GABA synthesis) showed altered hippocampal expression (largely down-regulation) in alcoholics and cocaine addicts. In contrast, with the exception of *GABRG2,* the other 8 genes loading onto factors 1 and 4 showed no changes in expression after chronic exposure to alcohol or cocaine.
Conclusions: Our results indicate that the $GABA_A$ gene clusters show both cis and trans correlations of gene expression. Moreover, the factor analysis revealed that distinct groups of genes, notably those involved in GABA synthesis and synaptic transport and the chr 4 cluster, previously associated with alcohol and drug dependence in humans, are sensitive to the effects of alcohol / cocaine. On the other hand the two factors on which the chr 15, chr X and most of the chr5 subunit genes loaded were impervious to alcohol / drug effects. These findings might have implications for therapeutic targets to combat stress-related craving and relapse.
Keywords: RNA-Seq; GABAA receptors; GABAB receptors; alcoholism; cocaine
Disclosure: M. Enoch, Nothing to Disclose; B. Baghal, Nothing to Disclose; Q. Yuan, Nothing to Disclose; D. Goldman, Nothing to Disclose.

T125. Caudate Activation Changes and Dose Response during Attention and Learning Tasks in Antipsychotic Treatment Studies of First Episode Schizophrenia

Sarah Keedy*, James Reilly, Margret Harris, Jeffrey R. Bishop, Peter Weiden, John Sweeney

University of Chicago, Chicago, Illinois

Background: Efficacy of antipsychotic medication for schizophrenia is linked to antagonism of D2 receptors in the caudate, crucial to circuitry supporting cognition and behavior. Effects of antipsychotics on the function of such circuitry involving the caudate are unclear and if better understood could provide insight into mechanisms of efficacy and varying treatment response. We have used the visually-guided saccade (VGS) task in fMRI studies before and after antipsychotic treatment in first episode schizophrenia, as the neural circuitry supporting this task is well established and includes the caudate. VGS assesses basic vigilance and sensorimotor responses (saccades) to visual stimuli. A variation is the predictive saccade (PS) task in which responses are generated from learned internal representations of spatial locations. It evokes similar circuitry as seen for VGS but with additional frontal and temporal lobe contributions which are of interest in schizophrenia.
Methods: Unmedicated first episode schizophrenia patients were scanned before and after 5 weeks of treatment (n = 12 risperidone; n = 2 aripiprazole). Matched healthy controls were scanned twice at a 5-week interval. At each scan, subjects performed VGS and PS in alternating 20 s blocks. In each block they followed a dot with their eyes as it relocated every 1 s. For VGS blocks, target location was unpredictable. For PS blocks, target location alternated between two positions, eliciting saccades which could precede

target appearance. Blocks of fixation were also presented for contrasting with the saccade blocks. We extracted subjects' activation for each saccade task in caudate as an *a priori* anatomically-defined region of interest, and in cortex activated by each task (e.g., frontal, supplemental, presupplemental, and parietal eye fields). We correlated activation with saccade latency, measured during the scans via an MRI-compatible eye tracker.
Results: Patients' dorsal visual attention cortex network (frontal, supplemental, parietal eye fields) was underactive relative to controls during both tasks pre- but not post-treatment, replicating prior findings in VGS and extending them to PS. Controls had significant positive correlations between latency and both cortex and caudate activation (Pearson r range: 0.5 – 0.6, $p<0.05$). Controls also had significant correlations between PS performance and supplementary eye field activation (baseline $r=-0.5$; follow-up $r=-0.8$, $p<0.05$), and right caudate activation at their second scan ($r=0.6$, $p<0.05$). By contrast, patients had no significant brain-behavior correlations prior to treatment. For VGS after treatment, both cortex and caudate activation correlated negatively with latency (r range: -0.6 - -0.71, $p<0.05$), an opposite relationship from that seen in controls. For PS, patients still had no significant activation-performance correlations after treatment. Change scores for caudate activation from pre to post treatment were significantly associated with performance change scores for VGS ($r=-0.7$, $p=.008$), and at a trend level for PS performance change ($r=0.5$, $p=.08$). Both tasks' change score correlations indicate greater caudate activation was associated with faster saccades. For PS, an additional trend was observed where a change to less dorsolateral prefrontal cortex activation from pre to post treatment was associated with worsened PS performance ($r=.51$, $p=.07$). Performance and change scores did not correlate with dose, but there was a positive correlation between risperidone dose and caudate activation at the post-treatment scan for both tasks (VGS $r=0.6$; PS $r=0.5$).
Conclusions: Although there was no significant or unitary direction of task-related caudate activation change from pre-to-post treatment, caudate activation changes were tightly linked to task performance changes. We specifically observed that greater caudate activation in patients was associated with faster saccade latencies, which we interpret as change toward abnormal performance (although patients were not different from controls for VGS latency). On the other hand, faster saccades during PS is a performance enhancement. Increased caudate activity could result in a net reduction of top-down control over brainstem saccade generators, operating in a more disinhibited state. Taken together, changes pre-to-post treatment were adverse or beneficial, depending on task goals and direction of activation change (e.g., by extension, those with decreased activation pre-to-post treatment had slower saccades and better VGS but worse PS performance). Risperidone dose was associated with greater task-related caudate activation, but this was independent of change scores or task performance, e.g., patients with the highest activation posttreatment were not necessarily those with the greatest increase from baseline activation levels. Hence, dose may have had a neurophysiological impact, but this was unrelated to the behavioral outcome that we assessed (latency). These findings demonstrate that links between brain and behavior can be discerned with sensitive methods such as the VGS task in fMRI studies, particularly given the significant brain-behavior correlations discernable in healthy subjects. Additional work is needed to identify individual differences such as pharmacogenetic markers that may explain variation in caudate activation changes after treatment.
Keywords: schizophrenia, first episode, risperidone, caudate, fMRI
Disclosure: S. Keedy, Nothing to Disclose; J. Reilly, Nothing to Disclose; M. Harris, Nothing to Disclose; J. Bishop, **Part 4:** Grant from Ortho-McNeil Janssen; P. Weiden, **Part 1:** Dr. Weiden is a consultant for and has received honoraria from Biovail, Delpor, Bristol Myers Squibb, Genentech/Roche, Lundbeck, Merck, Novartis, Ortho-McNeil Janssen, Otsuka, Pfizer Inc., and Sunovion, **Part 2:** Novartis, Ortho-McNeil Janssen, Pfizer, Sunovion, **Part 4:** Ortho-McNeil Janssen, Novartis, Sunovion; J. Sweeney, **Part 1:** Consultant to Takeda, Roche, Bristol-Myers Squibb, Lilly, Pfizer, **Part 4:** Grant from Ortho-McNeil Janssen.

T126. Buprenorphine Implants for the Treatment of Opioid Dependence: Six and 12 Month Outcomes

Katherine L. Beebe*, Steven Chavoustie, Walter Ling, Stacey Sigmon, Deborah Leiderman, Genie Bailey

Titan Pharmaceuticals Inc., San Francisco, California

Background: Subdermal buprenorphine hydrochloride/ethylene vinyl acetate implants represent a novel, abuse and diversion deterrent, sustained release formulation designed to deliver constant, low levels of buprenorphine (BPN) for up to six months for the treatment of opioid dependence. This formulation ensures patient compliance and substantially limits the problems with diversion and misuse commonly associated with existing forms of sublingual BPN. Across five completed Phase 3 studies, treatment with BPN implants has been shown to be well-tolerated and efficacious in significantly reducing illicit opioid use, retaining patients in treatment, controlling withdrawal symptoms and opioid cravings, improving global disease severity, and producing high overall patient satisfaction with therapy. The current report presents outcomes for patients treated for up to 12 months in two, sequential six-month clinical trials.
Methods: Study 1 was a six-month confirmatory efficacy and safety study in which 287 opioid-dependent adult outpatients were enrolled at 20 US sites. Following brief induction with sublingual BPN/naloxone tablets (12-16 mg/day), patients were randomized to receive either double-blind BPN implants, placebo implants, or open-label sublingual BPN tablets. A starting dose of four BPN implants (80 mg each) or placebo implants (EVA only) was administered subdermally in the inner, upper arms of patients assigned to these two treatment groups by clinicians who received specific training in the implant procedure techniques. The brief, in-office implant insertion and removal procedures were performed under local anesthetic using standardized equipment including a 10-gauge needle applicator for insertion and a modified vasectomy clamp for removal. A dose increase of one additional implant was permitted for patients who exceeded the protocol-specified allowance for rescue sublingual BPN. Urine samples were collected thrice weekly, and routine assessments of other clinical symptoms of opioid dependence and safety were conducted. Patients received regular drug counseling, and study completers were given the option of enrolling in Study 2, a six-month, open-label BPN implants re-treatment safety trial. Following the procedures to remove the BPN ($n=57$) or placebo ($n=8$) implants from Study 1, Study 2 participants ($N=85$) underwent brief re-induction with sublingual BPN 12-16 mg/day, and four BPN implants were inserted in the opposite arm. Twenty of the patients entering Study 2 were from the sublingual BPN treatment arm in Study 1 and received implants for the first time.
Results: In Study 1, treatment with BPN implants was clinically and statistically superior to placebo implants on the percentage of opioid-negative urines ($p<.0001$) and treatment retention (64% for BPN implants, 26% placebo, $p<.0002$), and was non-inferior to sublingual BPN in regard to reductions in opioid use. More than 80% of Study 1 completers requested the additional 6 months of treatment in Study 2. In Study 2, 79% completed, and patients treated with placebo implants or sublingual BPN during the initial 6-month treatment phase further decreased their self-reported drug use by an additional 25% and 20%, respectively when switched to BPN implants. At the end of 12 months of treatment with BPN implants, the majority of patients ($>90\%$) indicated that they were satisfied overall, including specifically with the implant insertion and removal procedures. In Study 1, implant site reactions were not significantly different in the BPN implant group (27.2% [31/114]) and placebo implant group (25.9% [14/54]). The most common implant site reactions were hematomas (7.0% for BPN implant 11.1% for placebo implant) and pain (5.3% for BPN implant and 9.3% for placebo implant). In Study 2, 12 of 85 subjects

(14.1%) experienced implant site reactions. The incidence of implant site adverse events was similar across all prior treatment groups (14.0%, 12.5%, and 15.0% of subjects who received BPN implants, placebo implants, and sublingual BPN, respectively). None of the implant site events were considered serious adverse events or led to study discontinuation. No evidence of implant removal or attempted removal was noted at any point during either of the two studies. Headache was the most common non-implant site related adverse event in the first study, for BPN implants (13.2% [15/114]) and sublingual BPN (16.0% [19/119]); insomnia (14.8% [8/54]) was the most common in the placebo implant group. There were no significant differences between BPN implant, sublingual BPN, and placebo implant on any of the adverse events. In Study 2, the most common adverse events were headache (11.8%), upper respiratory tract infection (8.2%), back pain (5.9%), and urinary tract infection (5.9%).
Conclusions: Results of these two studies confirm the 12-month safety and efficacy of BPN implants in the outpatient treatment of opioid dependence. Moreover, safety findings indicate that the in-office procedures specifically developed for implant insertion and removal are well-tolerated with relatively low risk of implant site adverse events. Implant site events that did occur were minor and did not lead to treatment discontinuation. These data, taken together with the demonstrated efficacy of BPN implants vs. placebo and non-inferiority relative to sublingual BPN, support the clinical use of this formulation in the treatment of opioid dependence.
Keywords: opioid dependence, buprenorphine, implant, randomized clinical trial, side effects
Disclosure: K. Beebe, **Part 1:** Dr. Beebe is an employee of Titan Pharmaceuticals, the company that is developing buprenorphine implants as a treatment for opioid dependence; S. Chavoustie, **Part 1:** Dr. Chavoustie has received consulting and review activity fees from Titan; W. Ling, **Part 1:** Dr. Ling has received unrestricted education grants and/or served as a consultant to Reckitt/Benckiser and research support from Reckitt/Benckiser, Hythiam Inc, US World Med, Titan, and DemeRx; S. Sigmon, Nothing to Disclose; D. Leiderman, **Part 1:** Provide Consultation Services to Johnson and Johnson PRD, Titan Pharmaceuticals and Astra Zeneca Pharmaceuticals, **Part 2:** Provide Consultation Services to Johnson and Johnson PRD, Titan Pharmaceuticals and Astra Zeneca Pharmaceuticals - All is consultation service income only, G. Bailey, **Part 1:** Dr. Bailey has received research support from the National Institute on Drug Abuse and Titan and Alkermes, and has received travel support to meetings from Titan.

T127. Does the MATRICS Consensus Cognitive Battery Detect Pro-cognitive Effects of Amphetamine in Healthy Adults?

Hsun-Hua Chou*, Jo A. Talledo, Sarah N. Lamb, Wesley K. Thompson, Neal R. Swerdlow

University of California, San Diego, La Jolla, California

Background: Cognitive deficits are a potent determinant of functional disability in schizophrenia. The cost of identifying and testing candidate pro-cognitive agents for schizophrenia is substantial. Conceivably, as a first screen, candidate drugs might be identified by positive effects on cognitive domains in sensitive subgroups of healthy subjects. Here, we examined whether the MATRICS Consensus Cognitive Battery (MCCB) detected pro-cognitive drug effects in specific subgroups of healthy individuals.
Methods: The effects of 20 mg amphetamine on MCCB performance were tested in a double-blind, placebo-controlled study of 60 healthy adults. Amphetamine effects were compared in subgroups of subjects characterized by relatively low vs. high baseline (placebo) MCCB scores, and by extreme values on specific personality subscales associated with schizophrenia-relevant biomarkers.
Results: Amphetamine exhibited potent autonomic (e.g. increased heart rate, systolic and diastolic blood pressure, all p's <0.0001) and subjective effects (e.g. reduced drowsiness, $p<0.04$), but did not significantly change MCCB composite scores or individual domain scores across the inclusive sample of 60 subjects (ANOVA: no significant main effects of AMPH dose ($F=1.39$, df 1,58, ns) or sex ($F<1$), and no interaction of AMPH dose x sex ($F<1$)). Amphetamine-induced MCCB changes were significantly (inversely) related to baseline MCCB performance: among individuals with lower baseline score, amphetamine increased MCCB performance, while among individuals with higher baseline scores, it did the opposite. ANOVA using a median split of baseline (placebo) performance produced a significant interaction of AMPH dose x baseline MCCB performance ($p<0.003$). This interaction reflected a significant AMPH-induced increase in MCCB Composite Score among subjects scoring in the lowest 50% of placebo values ($p<0.05$) and a significant AMPH-induced decrease in MCCB Composite Score among subjects scoring in the highest 50% of placebo values ($p<0.005$). Both baseline MCCB performance and amphetamine effects on MCCB scores were significantly related to specific personality domains associated with schizophrenia-linked genetic- and/or neurophysiological substrates.
Conclusions: Among healthy adults, amphetamine effects on MCCB performance were detected only among specific subgroups, and in specific cognitive domains. Strategies that utilize drug-induced changes in MCCB performance in healthy subjects to screen for candidate pro-cognitive drugs should consider the use of "enriched" subgroups with specific neurocognitive or personality characteristics. Additional design features to clarify the potential impact of regressions to the mean in within-subject drug challenge studies will be discussed.
Keywords: amphetamine, cognition, schizophrenia, MATRICS, neurocognition
Disclosure: H. Chou, **Part 4:** I received the APF/Merck Early Academic Career Award in May 2012; J. Talledo, Nothing to Disclose; S. Lamb, Nothing to Disclose; W. Thompson, Nothing to Disclose; N. Swerdlow, **Part 1:** I was a consultant for one afternoon, about a year ago, to Neurocrine, Inc.

T128. Advanced Paternal Age and DNA Methylation Abnormalities in Psychiatric Disease

Maria H. Milekic*, Yurong Xin, Anne O'Donnell, Kevin Kumar, John Edwards, Timothy Bestor, Victoria Haghighi, Jay A. Gingrich

New York State Psychiatric Institute/Columbia University, New York, New York

Background: Accumulating evidence from epidemiological studies support that advanced paternal age (APA) poses an increased risk in children for psychiatric disorders such as schizophrenia (SZ), bipolar and autism spectrum disorders (ASD). APA is one of the most significant risk factors for sporadic cases of SZ and ASD and the risk increases progressively when the father's age is 40 or older. Yet the causal mechanism by which paternal age increases the offspring risk remains unknown. The role of epigenetics in psychiatric disorders is poorly defined, but has been suggested to be an important factor given the genetic complexity of the disorders. Epigenetic mechanisms play a critical role in several biological processes of importance to human health and DNA methylation abnormalities have been observed in the psychiatric disorders associated with APA. DNA methylation during spermatogenesis is an active process, which is susceptible to errors that can be propagated to subsequent generations. We hypothesized that DNA methylation abnormalities arising in the sperm of older fathers are inherited by the offspring and result in altered gene expression and behavior.
Methods: Old (12mo) and young (3mo) male 129SvEv mice were paired with two female (3mo) 129SvEv mice to generate old (OFO) and young (YFO) father offspring. The males were removed after 2 weeks to prevent direct contact with the offspring and the females were separated to control for maternal and litter effects. At 3mo the offspring were tested on a behavioral battery, which included tasks such as open field, startle activity, active avoidance and social interaction. We

determined DNA methylation using a whole genome high throughput sequencing approach called Methylation Mapping Analysis by Paired-end Sequencing (Methyl-MAPS) (Edwards et al. *Genomic Res.* 2010). Epididymal sperm from old and young fathers was collected after breeding them and the brains of the offspring were harvested at the end of behavioral testing. For the methylation studies we used offspring (n = 4/group) with behavioral performance ±1.5 S.D. from the mean and their respective fathers. Genomic DNA was isolated, digested with either methylation-sensitive (AciI, HhaI, HpaII, HpyCH4IV and BstUI) or –dependent (McrBC) enzymes and mate-paired libraries were prepared for sequencing on the SOLiD platform (ABI). Data was processed and analyzed as previously described by Xin et al. (*Epigenetics*, 2011).

Results: To investigate whether aging alters sperm DNA methylation patterns, we performed genome-wide methylation profiling of epididymal sperm DNA pooled from 3-month-old (n = 4) or 12-month-old (n = 4) mice using Methyl-MAPS. Mapping the methylation difference between the two groups across the regions up- and downstream of the transcription start site (TSS) and the first, internal and last exons of all 20,496 Refseq genes, we found that old mice had a significant loss of methylation at the regions flanking the TSS compared to young males. Comparing CpG island (CGI) and non-CGI promoters, the methylation difference was more profound at the regions up- and downstream of CGI promoter, so called CGI shores. In addition, we observed significant hypomethylation in old mice at splice junctions. Behavioral testing of the offspring of these old and young males revealed that OFO have significantly reduced exploratory, startle amplitude and prepulse inhibition compared to YFO. Performing Methyl-MAPS on brain DNA from OFO and YFO we found that, similar to the old fathers, OFO have significantly reduced DNA methylation at the regions flanking the TSS. This difference was specific to promoter CGI shores, as the methylation of OFO and YFO at non-CGI promoters appeared to be the same. This suggests that DNA methylation abnormalities arising in the sperm of the fathers are passed on to the offspring and result in altered gene expression that leads to behavioral abnormalities.

Conclusions: Similar to the epidemiological findings in humans, we found that increased paternal age in mice is associated with behavioral impairments in the offspring. This seems to be mediated, at least in part, by germ line transmission of DNA methylation abnormalities arising in the sperm of older fathers. Our whole genome methylation experiments on sperm DNA from old and young male mice, revealed that there is hypomethylation of promoter CGI shores with aging and that this specific signature is also present in the OFO. These CGI shores have been shown to contain cell-, tissue- and species specific DNA methylation differences (Irizarry, Nat. Genet, 2009; Xin et al., *Epigenetics*, 2012). Experiments are currently under way to determine whether the methylation changes observed in the brains of the offspring result in aberrant gene expression that may underlies the behavioral abnormalities. It is our hope that these findings will inform our understanding of the pathophysiology of ASD and SZ, eventually leading to the development of new and more effective therapeutic interventions.

Keywords: Paternal age, animal model, epigenetics, schizophrenia, autism

Disclosure: M. Milekic, Nothing to Disclose; Y. Xin, Nothing to Disclose; A. O'Donnell, Nothing to Disclose; K. Kumar, Nothing to Disclose; J. Edwards, Nothing to Disclose; T. Bestor, Nothing to Disclose; V. Haghighi, Nothing to Disclose; J. Gingrich, Nothing to Disclose.

T129. Distinguishing Bipolar Disorder from Major Depressive Disorder in Adolescents: An FMRI Study

Jill Russo, Fei Wang, Hilary Blumberg*

Yale School of Medicine, New Haven, Connecticut

Background: Elucidation of neural circuitry differences between bipolar disorder (BD) and major depressive disorder (MDD) in adolescence could be important in developing improved methods for detection, and understanding of pathophysiology to develop improved early treatment interventions to reduce suffering and improve prognosis. Abnormalities in amygdala responses to positive emotional stimuli have been theorized to be especially salient in BD in adolescents, given the unique vulnerability to extremes of positive affective states in the disorder, findings in adults with BD and MDD, and the previous findings of amygdala abnormalities in adolescents with mood disorders.

Methods: Subjects included adolescents ages 14-18 years: 25 with BD (mean age 16.2 +/− 1.0 years), 25 with MDD (16.4 +/− 1.2 years) and 24 healthy comparison adolescents (16.0 +/− 2.0 years) without a personal history or first degree relative with a major mood or psychotic disorder. The adolescents participated in functional magnetic resonance imaging (fMRI) while processing faces depicting happy, fearful or neutral expressions.

Results: The adolescents with BD were distinguished from the adolescents with MDD by the presence of increased activation of the amygdala during the processing of happy face stimuli ($p < 0.005$). Findings also included group differences observed in additional corticolimbic regions that showed both state- and stimulus- dependent features.

Conclusions: The results support the potential importance of the amygdala, and particularly of amygdala responses to positive emotional stimuli, in distinguishing BD from MDD in adolescents.

Keywords: bipolar disorder, depression, adolescent, fmri

Disclosure: J. Russo, Nothing to Disclose; F. Wang, Nothing to Disclose; H. Blumberg, Nothing to Disclose.

T130. Pre-attentive Information Processing and Impulsivity in Bipolar Disorder

Alan C. Swann*, Marijn Lijffijt, Scott Lane, Joel Steinberg, F. Gerard Moeller

The University of Texas Health Science Center at Houston, Houston, Texas

Background: Encoding and filtering (gating) before conscious awareness of a stimulus may reduce overstimulation and facilitate conformation of responses to their context. Yet, behavioral correlates of sensory gating are not well understood. Because sensory gating represents failure to suppress responses to an inappropriate stimulus, gating may be related to behavioral response inhibition. Auditory gating is impaired, and impulsivity is prominent, in bipolar disorder. We compared pre-attentional and early attentional evoked potentials (EP) in bipolar disorder and healthy controls, and investigated relationships to impulsivity in bipolar disorder.

Methods: There were 48 healthy controls without family histories of mood disorders and 48 subjects with bipolar I disorder. Impulsivity was measured by laboratory tasks (Immediate Memory Task measuring rapid-response impulsivity and Two-Choice Paradigm measuring reward-based impulsivity) and questionnaire (Barratt Impulsiveness Scale-11). EP was measured by latencies, amplitudes, and gating for auditory P50 (pre-attentional), N100 (initial direction of attention) and P200 (initial conscious awareness), using a paired-click paradigm, where S1 and S2 were identical stimuli 0.5 sec apart. Gating was considered the ability to suppress responses to S2. Analyses used repeated-measures general linear models.

Results: P50 S1 amplitude correlated with accurate laboratory-task responding, and was lower in bipolar disorder than in controls. S2 amplitude correlated with impulsive task performance and fast reaction times in subjects with bipolar disorder. N100 and P200 gating were reduced in bipolar disorder, but did not correlate with impulsivity. These findings were independent of symptoms, treatment, or substance-use history. EPs were not related to questionnaire-measured or reward-based impulsivity in bipolar disorder.

Conclusions: In bipolar I disorder, pre-attentional information processing reflects reduced orientation to the stimulus relative to

controls. Within bipolar disorder, rapid-response impulsivity correlates with impaired response suppression.
Keywords: bipolar disorder; neurophysiology; impulsivity; attention; sensory gating
Disclosure: A. Swann, Nothing to Disclose; M. Lijffijt, Nothing to Disclose; S. Lane, Nothing to Disclose; J. Steinberg, Nothing to Disclose; F. Moeller, **Part 1:** Boehringer Ingelheim (Consultant).

T131. Extracellular Matrix Abnormalities in Olfactory Epithelium Tissue from Subjects Diagnosed with Schizophrenia

Harry Pantazopoulos, Anne Boyer-Boiteau, Steven E. Arnold, Sabina Berretta*

McLean Hospital - Harvard Medical School, Belmont, Massachusetts

Background: Growing evidence points to extracellular matrix (ECM) abnormalities in the pathophysiology of schizophrenia (SZ). Among other findings, markedly abnormal expression of chondroitin sulfate proteoglycans (CSPGs), a main ECM component, was observed in the medial temporal lobe of subjects with SZ. CSPG functions during development are highly relevant to the pathophysiology of SZ, a neurodevelopmental disorder thought to involve disruption of neuronal migration and connectivity. A compelling example of the role that CSPGs play in brain development is found in the olfactory epithelium (OE) and its connections with the olfactory bulb. In this unique part of the CNS, neuron differentiation, migration and axon outgrowth occur robustly throughout life. With the present study we tested the hypothesis that CSPG expression in OE may be altered in SZ.
Methods: Histochemically-labeled CSPG-positive cells were counted in postmortem OE from non-psychiatric control (n = 9) and SZ (n = 10) subjects using computer-assisted light microscopy. Dual antigen immunofluorescence on OE biopsy (n = 2) and postmortem OE tissue (n = 1) from normal control subjects was used to test whether distinct patterns of CSPG expression were observed in mature and immature olfactory receptor neurons (ORN).
Results: Diffuse CSPG labeling within the cytoplasm was detected in sustentacular cells and a group of ORNs (c-CSPG + ORNs), while cell surface, 'pericellular' CSPG labeling was found in basal cells and a distinct group of ORNs (p-CSPG + ORNs). Dual labeling for CSPG and markers for mature and immature ORNs suggests that c-CSPG + ORNs and p-CSPG + ORNs correspond to mature and immature ORNs, respectively. Numerical densities of c-CSPG + ORNs were significantly decreased in SZ ($p < 0.025$; 99.32% decrease). Numerical density changes of p-CSPG + ORNs (110.71% increase) and CSPG + basal cells (53.71% decrease), did not reach statistical significance. However, the ratio of p-CSPG + ORNs/ CSPG + basal cells was significantly increased ($p = 0.03$) in SZ.
Conclusions: The present results show that CSPGs abnormalities are present in the OE of SZ subjects. In particular, numerical density of c-CSPG + ORNs, putatively corresponding to mature ORNs, is significantly decreased in the OE of subjects with SZ. We postulate that this decrease may reflect a reduction of c-CSPG expression in mature ORNs. This reduction may be due to decreased synthesis and/or to failure of these cells to fully mature to an adult pattern of CSPG expression. This latter possibility is supported by significantly increased ratio of p-CSPG + ORNs / CSPG + basal cells, consistent with previous findings by Arnold et al. (Arnold et al., 2001). Given the role CSPGs play in OE cell differentiation and axon guidance from OE into the olfactory bulb, we suggest that altered CSPG expression may contribute to ORN lineage dysregulation and olfactory identification abnormalities observed in SZ.
Keywords: schizophrenia, olfactory epithelium, extracellular matrix, proteoglycans
Disclosure: H. Pantazopoulos, Nothing to Disclose; A. Boyer-Boiteau, Nothing to Disclose; S. Arnold, Nothing to Disclose; S. Berretta, Nothing to Disclose.

T132. A Specific Blood Gene Expression Pattern is Correlated with a Neurophysiological Abnormality in Deficit Syndrome of Schizophrenia

Yasushi Kajii*, Ikwunga Wonodi, Elliot Hong, Gunvant K. Thaker

Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan

Background: Effective management of negative symptoms and cognitive deficits in schizophrenia is a key issue for improving functional outcomes and current medications cannot meet this need. Indeed, around 25% of schizophrenia patients show severe primary and persistent negative symptoms called the deficit syndrome. Hereditary neurophysiological traits, including abnormal eye tracking, are also commonly observed in deficit syndrome schizophrenia as corresponding endophenotypes. Here we tried to find biological markers (BMs) in the blood associated with the endophenotypes and to postulate a specific biological pathway including the BMs.
Methods: Whole blood samples from three groups of ten subjects (deficit patients, non-deficit schizophrenia patients and age-matched controls) were drawn in the morning into PAXgene tube and total RNA was obtained by a standard method. Transcriptome data of the samples were generated by Affymetrix GeneChip and heatmap analysis was done using statistically significant probes for deficit syndrome. Neurophysiological endophenotype data of all thirty subjects were obtained and quantitative correlation to the gene expression levels was analyzed.
Results: We found five Affymetrix probes whose expression levels were specifically augmented in the deficit group ($p < 0.01$ vs normal control and non-deficit schizophrenia groups, Tukey test, n = 10). Additionally, correlation of their expression levels with the value of predictive pursuit endophenotype, which was specifically impaired in deficit patients, was quite robust ($p = 0.0001$ - 0.0135). On the other hand, other endophenotypes such as PPI were not so tightly correlated. By combination of the expression data, a group of subjects, whose eye tracking properties were unusual, was clearly segregated and nine of the ten deficit patients were included in this specific group. None of controls or non-deficit subjects was categorized in the same group of deficit. Therefore, they seemed to be useful as BM for deficit syndrome. The specific probes contained three known functional genes for MAP kinase-interacting serine/threonine-protein kinase 1 (MKNK1), tripartite motif containing 8 (TRIM8) and toll-like receptor 5 (TLR5). Search for functional networks involving them indicated modification of an immune-responding system leading to cytokine release and the kynurenine pathway of tryptophan metabolism.
Conclusions: Although the present study is limited by small sample size, resulting data demonstrate that deficit patients with a clear neurophysiological abnormality have different properties of biological systems even in peripheral BM profiling. The TLR5-TRIM8-MKNK1 signaling pathway could regulate cytokine release such as IL-1b and IL-6, whose induction is suggested to be associated with schizophrenia, through elongation initiating factors (eIFs). Quite interestingly, toll-like receptor systems including TLR5 are recently reported to be linked to the kynurenine pathway (Clarke G et al. Fron Pharmacol 3, 1-9, 2012). We also reported the link between the kynurenine pathway and cognitive impairment in schizophrenia (Wonodi et al. Arc Gen Psychiatry 68, 665-674, 2011). Imbalance of the kynurenine pathway is thought to cause dysregulation of glutamatergic and cholinergic neurotransmissions (Wonodi and Schwarcz. Schizophr Bull 36, 211-218, 2010). Therefore, our new finding here suggests another possibility of immune-related pathways being involved in negative symptom-related functional abnormality.
Keywords: Schizophrenia, deficit syndrome, cognitive deficits, endophenotypes, immune activation, cytokines, biomarkers
Disclosure: Y. Kajii, **Part 1:** Mitsubishi Tanabe Pharma Corporation, **Part 2:** Mitsubishi Tanabe Pharma Corporation, **Part 3:** Mitsubishi Tanabe Pharma Corporation, **Part 4:** Mitsubishi Tanabe Pharma Corporation; I. Wonodi, Nothing to Disclose; E. Hong, Nothing to Disclose; G. Thaker, Nothing to Disclose.

T133. Neurocognitive Functioning and Impairment in Awareness of Illness in Schizophrenia: Baseline Correlations and Treatment Effects

Philip D. Harvey*, Cynthia Siu, Josephine Cucchiaro, Andrei Pikalov, Antony Loebel

University of Miami Miller School of Medicine, Miami, Florida

Background: Lack of insight in schizophrenia was first described in terms of reduced awareness of the presence and significance of psychotic symptoms. However, unawareness is frequently associated with deficits in self-assessment of cognitive and functional abilities, as well as outcome of rehabilitation-oriented interventions. The relationship between reduced awareness of illness and the ability to perform cognitive tests was evaluated in a controlled clinical study. The extent to which treatment-related improvement in awareness was related to improvement in cognition was also examined.
Methods: Patients with acute exacerbation of Lack of insight in schizophrenia was first described in terms of reduced awareness of the presence and significance of psychotic symptoms. However, unawareness is frequently associated with deficits in self-assessment of cognitive and functional abilities, as well as outcome of rehabilitation-oriented interventions. The relationship between reduced awareness of illness and the ability to perform cognitive tests was evaluated in a controlled clinical study. The extent to which treatment-related improvement in awareness was related to improvement in cognition was also examined.schizophrenia were randomized to once-daily treatment with lurasidone 80 mg (N = 125, LUR80), lurasidone 160 mg (N = 121, LUR160), quetiapine XR 600 mg (N = 120, QXR) or placebo (N = 122, PBO) in a 6-week, double-blind study, followed by a 6-month, double-blind extension. Cognitive performance was examined with the computerized CogState system and functional capacity was assessed with the UPSA-B at baseline, after 6 weeks, and at 3 and 6 months in the extension phase. Impairment of insight was assessed by PANSS item G12 "lack of judgment and insight" at baseline and at each of the post-randomization visits.
Results: A total of 481 patients (7753 CogState battery neurocognitive assessments) were tested during the acute phase. Of these assessments, 1355 neurocognitive tests failed the completion or prespecified evaluability criteria (n = 214 patients). In this non-evaluable cohort, baseline total PANSS scores, insight scores (G12), and neurocognitive composite scores were 101.4 (SD 11.1), 3.9 (SD 1.0, median 4), and z = −7.9 (SD 2.6), respectively, compared to normative standards. The remaining two hundred and sixty-seven patients provided evaluable neurocognitive composite scores at both baseline and week 6 assessments (LOCF), with the proportion of subjects with evaluable domain Z-scores ranging from n = 228/481 (47%) for the visual learning task to n = 393/481 (82%) for the verbal learning task. Lower levels of impairment in insight at baseline predicted increased likelihood of completion of the study and an increased likelihood of providing evaluable neurocognitive testing scores at 6 weeks ($p <= 0.002$) in the full ITT sample (N = 481). In patients whose testing results met the prespecified evaluability criteria (n = 267), LUR160 was superior to both placebo ($p = 0.038$) and quetiapine XR ($p = 0.018$) for the composite cognitive functioning measure at week 6. Compared to placebo, patients receiving LUR160 also had superior performance in the verbal learning ($p = 0.04$), social cognition ($p < 0.01$), and memory delayed recall domains ($p = 0.02$). In contrast, treatment with QXR, led to significant worsening in attention/vigilance domains, but not the total score, when comparing to placebo. PANSS total and Insight item scores were significantly improved in LUR160, LUR80 and QXR compared to placebo. Improved insight (lower PANSS item G12 scores) during the acute phase was a significant mediator for the effect of LUR160 (vs. placebo) on the neurocognitive composite score ($p < 0.05$), UPSA-B total score ($p < 0.05$), and the domain scores for verbal learning ($p < 0.05$) and social cognition ($p < 0.05$) but not for delayed recall memory ($p = 0.339$), during the acute treatment period.
Conclusions: Lower insight predicted reduced ability to validly complete cognitive assessments. Conversely, gain in insight predicted improvements in cognitive functioning and performance-based measures of functional capacity. These results suggest that even objective performance-based assessments can be affected by changes in awareness of illness, consistent with prior research in this area. Although the current findings suggest that gain in insight is associated with improved cognitive and functional capacity, the directionality of this change remains to be established. Future research will need to examine the extent to which impaired awareness impacts the willingness to accept treatments for cognitive and functional deficits and the extent to which these deficits can be ameliorated by direct interventions.
Keywords: Schizophrenia; neurocognition; insight
Disclosure: P. Harvey, **Part 1:** Abbott Labs, Amgen, Boeheringer Ingelheim, Bristol-Myers-Squibb, Forest Labs, Genentech, Johnson and Johnson, Roche Pharma, Shire Pharma, Sunovion Pharma, Takeda Pharma, **Part 2:** Pharma Neuroboost, **Part 4:** Astra-Zeneca; C. Siu, **Part 1:** Pfizer, Sunovion Pharma, **Part 2:** Pfizer, Sunovion Pharma, **Part 3:** Pfizer, Sunovion Pharma; J. Cucchiaro, **Part 1:** Sunovion Pharma, **Part 2:** Sunovion Pharma, **Part 3:** Sunovion Pharma; A. Pikalov, **Part 1:** Sunovion Pharma, **Part 2:** Sunovion Pharma, **Part 3:** Sunovion Pharma; A. Loebel, **Part 1:** Sunovion Pharma, **Part 2:** Sunovion Pharma, **Part 3:** Sunovion Pharma.

T134. N-acetylcysteine in the Treatment of Pediatric Trichotillomania: A Randomized, Double-blind, Placebo-controlled Trial

Michael Bloch*, Kaitlyn Panza, Jon E. Grant, James Leckman, Christopher Pittenger

Yale University Medical School, New Haven, Connecticut

Background: N-acetylcysteine (NAC) is an over-the-counter supplement that acts as an antioxidant and a glutamate modulating agent. A randomized, placebo-controlled trial demonstrated the efficacy of NAC in the treatment of adults with trichotillomania (TTM). The goal of the current study was to examine the efficacy of NAC for the treatment of pediatric TTM in a double-blind, placebo-controlled study.
Methods: Thirty-nine children aged 8-17 years with pediatric trichotillomania were randomly assigned to receive NAC or matching placebo for 12 weeks. Our primary outcome was change in severity of hairpulling as measured by the Massachusetts General Hospital Hairpulling Scale (MGH-HPS). Secondary measures assessed hairpulling severity, automatic vs. focused pulling, clinician-rated improvement and comorbid anxiety and depression. Outcomes were examined using linear mixed models to test the treatment x time interaction in an intention-to-treat population.
Results: No significant difference between N-acetylcysteine and placebo was found on any of the primary or secondary outcome measures. On several measures of hairpulling, subjects significantly improved with time regardless of treatment assignment. Twenty-five percent of subjects in the NAC group were judged as treatment responders compared to 21% in the placebo group.
Conclusions: We observed no benefit of NAC for the treatment of children with trichotillomania. Our findings stand in contrast to a previous, similarly designed trial in adults with TTM, which demonstrated a very large, statistically significant benefit of NAC. Based on the differing results of NAC in pediatric and adult TTM populations, the assumption that pharmacological interventions demonstrated to be effective in adults with TTM will be as effective in children, may be inaccurate. This trial highlights the importance of referring children with TTM to appropriate behavioral therapy before initiating pharmacological interventions, as behavioral therapy has demonstrated efficacy in both children and adults with trichotillomania.
Keywords: trichotillomania, children, n-acetylcysteine, clinical trial
Disclosure: M. Bloch, Nothing to Disclose; K. Panza, Nothing to Disclose; J. Grant, **Part 1:** Psyadon Pharmaceuticals, **Part 4:** Psyadon Pharmaceuticals; J. Leckman, Nothing to Disclose; C. Pittenger, Nothing to Disclose.

T135. Evidence of an Inflammatory Pathway Leading to Psychosis in Bipolar Disorder

Mikael Landén*, Carl Sellgren, Magdalena Kegel, Carl-Johan Ekman, Patrick Sullivan, Jordan W. Smoller, Pamela Sklar, Göran Engberg, Sophie Erhardt

The Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden

Background: Family history is the strongest risk factor for bipolar disorder. Yet it has been difficult to identify susceptibility gene variants. An alternative approach to unearth causal genetic mutations is to focus on biomarkers, i.e., measurable key components in biological pathways between genotype and disease. We therefore conducted a genome wide association study (GWAS) of kynurenic acid (KYNA) in cerebrospinal fluid (CSF), based on that elevation of KYNA in brain is a consistently found biochemical aberration in psychotic disorders. We then studied the genetic finding in relation to psychotic symptoms, cognition, and brain gray matter volume. Lastly, we used an *in vitro* model to test if IL-1b is the link between the genetic variant and elevated CSF levels of KYNA.
Methods: CSF was collected from patients with bipolar disorder (N = 76) and a genome-wide association study in relation to CSF KYNA was conducted. Patients underwent magnetic resonance imaging (MRI) scans of the brain and a neurocognitive test battery. Human cortical astrocytes were cultured and stimulated with recombinant human IL-1b (10 ng/ml). Analysis of KYNA was performed using an isocratic reversed-phase high-performance liquid chromatography (HPLC) system.
Results: One SNP located on chromosome 1 reached genome-wide statistical significance in relation to CSF KYNA (rs10158645, b = 1.05, $P = 3.85x10^{-8}$, MAF = 0.15). The minor allele of rs10158645 was associated with increased risk of psychotic features ($n = 76$, OR = 4.0, 95%CI:1.4-12), increased verbal working memory ($n = 108$, b = 1.8, $P = 0.019$) and increased gray matter thickness in corresponding brain regions ($n = 138$, P = 0.02, voxel-level FWE-corrected) the *in vitro* results showed that IL-1b increases KYNA levels in human cortical astrocytes by inducing the rate-limiting enzyme TDO2.
Conclusions: The minor allel of rs10158645 has previously been coupled to a decreased expression of sortin nexin 7 (SNX7), which in turn activates caspase-8 that increases IL-1β. Here we found that IL-1β stimulates KYNA, known to be increased in psychotic disorders. This raises the possibility that SNX7-induced IL-1b dependent activation of the kynurenine pathway is a molecular pathway underlying psychosis in bipolar disorder.
Keywords: Bipolar disorder, kynurenic acid, cerebrospinal fluid, genome wide association study
Disclosure: M. Landén, Nothing to Disclose; C. Sellgren, Nothing to Disclose; M. Kegel, Nothing to Disclose; C. Ekman, Nothing to Disclose; P. Sullivan, Nothing to Disclose; J. Smoller, Nothing to Disclose; P. Sklar, **Part 1:** Pfizer-1 day consultation/meeting Feb 2011; G. Engberg, Nothing to Disclose; S. Erhardt, Nothing to Disclose.

T136. Psychometric Evaluation of the Brown Assessment of Beliefs Scale in Body Dysmorphic Disorder and Obsessive-compulsive Disorder

Katharine A. Phillips*, Ashley S. Hart, Jane L. Eisen, William Menard, Nicholas J. Sibrava, Steven Rasmussen

Alpert Medical School of Brown University; Rhode Island Hospital, Providence, Rhode Island

Background: Delusionality/insight is an important dimension of psychopathology that is relevant to treatment outcome in many psychiatric disorders, such as mood disorders, schizophrenia, obsessive-compulsive disorder (OCD), body dysmorphic disorder (BDD), and eating disorders. The Brown Assessment of Beliefs Scale (BABS) is a 7-item, semi-structured, rater-administered scale that assesses delusionality/insight both dimensionally and categorically (e.g., delusional vs. nondelusional) across a range of disorders. The BABS has been widely used in studies of OCD and BDD. It has been shown to have strong reliability, validity, and sensitivity to change in OCD, BDD, and psychotic depression, as well as strong reliability and validity in schizophrenia/schizoaffective disorder. However, sample sizes in these studies were relatively small. This report examines the BABS's psychometric properties in larger samples of OCD and BDD subjects.
Methods: 327 BDD subjects ($n = 191$ from a BDD course of illness study and $n = 136$ from BDD medication studies) and 302 OCD subjects from a course of illness study were interviewed with the BABS to assess insight regarding disorder-specific beliefs (e.g., "I look deformed" in BDD, and "If I don't check the stove over and over, the house will burn down" in OCD). Subjects were also administered the BDD-YBOCS or Y-BOCS (measures of current BDD and OCD severity, respectively), the 17-item HAM-D (current depressive symptoms), and the BPRS (severity of overall psychopathology, in BDD subjects only). BABS psychometric properties were examined.
Results: Mean BABS total score reflected poor insight in the BDD sample (15.7 ± 6.0 for the full sample; 16.4 ± 5.3 for the 308 subjects with current BDD) and good insight in the OCD sample (6.5 ± 5.1 for the full sample; 7.2 ± 5.0 for the 249 subjects with current OCD). BDD sample results*: In the BDD sample, ICCs demonstrated good interrater reliability across 2 raters ($n = 23$) for BABS total score (.97) and individual items (.68 to .99; median = .96, all p's < .001). Cronbach's alpha coefficient was .87, indicating good internal consistency. Correlations between each item and the total score minus that item were $r = .40$ to .83 (median = .69, all p's < .001). The test-retest ICC ($n = 32$) over one week was .93 for BABS total score and .63 to .91 (median = .77, all p's < .001) for individual items. Principal components factor analysis using varimax rotation identified 1 factor accounting for 60% of the variance (factor loadings were .51 to .91). Regarding discriminant validity, BABS total score was significantly and positively correlated with BDD-YBOCS total score ($r = .59$, $p < .001$) and with HAM-D total score ($r = .25$, $p < .001$); however, BDD and depressive symptom severity accounted for only 35% and 6% of the variance in BABS total score, respectively. BABS total score was not significantly correlated with BPRS total score ($r = .22$, $p = .08$). Among BDD subjects who received SRI treatment in medication studies ($n = 88$), the mean BABS score significantly decreased from baseline to post-treatment ($t = 8.7$, $p < .001$), indicating sensitivity to change. OCD sample results*: Cronbach's alpha coefficient was .80, indicating good internal consistency. Correlations between each item and the total score minus that item were $r = .34$ to .75 (median = .49, all p's < .001). Principal components factor analysis using varimax rotation identified 1 factor accounting for 47% of the variance (factor loadings were .47 to .87). Regarding discriminant validity, BABS total score correlated $r = .53$ ($p < .001$) with Y-BOCS total score and $r = .36$ ($p < .001$) with HAM-D total score; however, OCD and depressive symptom severity accounted for only 28% and 13% of the variance in BABS score, respectively.
Conclusions: These findings provide further evidence that the BABS is a reliable and valid measure of delusionality/insight in OCD and BDD. It is suitable for use in treatment studies. Further research on this scale's psychometric properties is needed in other disorders.
Keywords: Body Dysmorphic Disorder, Obsessive-Compulsive Disorder, assessment, delusionality, insight
Disclosure: K. Phillips, **Part 1:** American Foundation for Suicide Prevention (research funding); Forest Laboratories (medication only for a study sponsored and funded by the National Institute of Mental Health); Transcept Pharmaceuticals (research funding); Oxford University Press; Elsevier; Merck Manual (future); Guilford Press (potential future royalties); The Free Press (potential future royalties), **Part 2:** American Foundation for Suicide Prevention (research funding); Forest Laboratories (possibly; exact value of medication in each year is unknown); Transcept Pharmaceuticals, **Part 4:** American Foundation for Suicide Prevention (research funding); Forest Laboratories (medica-

tion for NIH-funded study); Transcept Pharmaceuticals (research support); A. Hart, Nothing to Disclose; J. Eisen, Nothing to Disclose; W. Menard, Nothing to Disclose; N. Sibrava, Nothing to Disclose; S. Rasmussen, Nothing to Disclose.

T137. Polymorphisms within PP-fold Polypeptide Pathway May Contribute to Susceptibility of Eating Disorders and Related Endophenotypes

Pei-an Betty Shih*, Nicholas Schork, Wade Berrettini, Andrew Bergen, Pierre Magistretti, Cinnamon Bloss, Ashley Van Zeeland, Walter Kaye

University of California San Diego, San Diego, California

Background: Peptide YY (PYY) and Neuropeptide Y (NPY) are neuroendocrine PP-fold polypeptides that bind to NPY receptors to regulate satiety and stress response. We have previously shown that CSF PYY was significantly higher in BN than that of restricting anorexia nervosa (ANR) or healthy controls (HC), whereas CSF PYY was not different comparing to ANR, binge/purge anorexia nervosa (ANBP), or HC. On the other hand, CSF NPY was significantly higher in underweight ANBP compared to weight-restored patients, but it was not different between BN and HC. These data suggest that ED subtypes may hold differences in NPY and PYY functions of which constitute pathophysiological distinctions between the subtypes. We aimed to further test these hypotheses through investigation of single nucleotide polymorphisms (SNPs) within the two peptides and their principle receptors. Using an existing eating disorder (ED) candidate gene study dataset, we selected genes coding for these 2 peptides (*PYY*, *NPY*) and 2 NPY receptors (*NPY1R, NPY2R*) to explore whether patterns of genetic association with eating disorder (ED) and related subtypes may be informative regarding differentiation of the three clinical ED subtypes. Furthermore, we conducted marker-on-trait association analysis with the ED endophenotypes in anorexia nervosa and bulimia nervosa to see if trait-associated genetic markers overlap between these two major disorder subtypes.
Methods: The subjects were 419 patients with ANR, 660 patients with ANBP, 110 patients with BN, and 677 age-matched women HC. Lowest lifetime body mass index (LBMI) during the ED duration was used as a proxy for disease severity. Personality trait perfectionism, harm avoidance, novelty seeking, and anxiety scores were used as intermediate phenotypes of ED for marker-on-trait association analysis. 24 SNPs were chosen from these 4 pathway genes and genotyped using Illumina Infinium platform. SNP-by-SNP interaction analyses were conducted using multifactor-dimensionality reduction method (MDR), haplo.stats package was used for haplotype analysis. T-test, Chi-square, and ANOVA with age as a covariate were applied for association analyses using R vs.2.14.2.
Results: Haplotype analysis showed no evidence of individual gene-based association with risk of ED or with either ANR, ANBP, or BN subtype. One *NPY1R* 3′-UTR SNP was found to be associated with ED ($p = 0.02$). Epistasis analysis revealed interaction between a *PYY* Arg72Thr SNP and *NPY1R* 3′-UTR SNP to be associated with ED risk. Additional epistasis analyses revealed that interactions of *PYY* Arg72Thr and *NPY1R* 3′-UTR SNP and *NPY* promoter SNP and *NPY1R* 3′-UTR SNP were associated with ANR and ANBP subtypes, respectively. However, the interaction between *PYY* Arg72Thr SNP and *NPY2R* promoter SNP was most significantly associated with the BN subtype. *NPY2R* Ile195 SNP genotypic frequency was found to be significantly different across the 3 ED subtypes ($p = 0.04$). Using LBMI as disease severity marker, significant associations were observed between 2 *NPY1R* SNPs (3-UTR and intronic SNP) and LBMI in the BN subtype ($p = 0.001$ for both SNPs) but no evidence of SNP effect on LBMI was observed in ANR or ANBP subtypes. There were significant differences in score of ED endophenotypes between the ANR and BN subtypes. Stratified by these two subtypes, SNPs within *PYY* and *NPY2R* genes were significantly associated with perfectionism ($p = 0.01$–0.03) only in BN but not in ANR, SNPs in *PYY* and *NPY2R* were associated with novelty seeking only in ANR ($p = 0.009$-0.04) but not in BN subtype, and a *PYY* SNP was associated with state anxiety only in ANR ($p = 0.03$) but not in BD.
Conclusions: Using a biological peptide-receptor pathway investigation approach, our results raised the possibility that each individual subtype may be under the influence of differing genetic interactions of which may also represent the *in vivo* peptide-receptor interactions. That is, susceptibility of ANR and ANBP seems to be under the influence of *NPY1R* interaction with peptide ligands, whereas susceptibility to BN appears to be affected by *NPY2R*-related functions. Moreover, marker-on-trait associations with endophenotypes in the ED subtypes demonstrated differential patterns of associations in ANR versus BN subtypes, suggesting that restricting anorexia and bulimia patients may harbor different genetic susceptibility that influence their behavior traits. Because NPY and PYY have powerful effects on appetite, they are potential candidates for understanding ED pathology. While the findings are modest, and require replication, they raise some possibility that genetic variation within a pathway relating to stress and appetite biology may be potential biomarkers for ED subtypes.
Keywords: Anorexia Nervosa, Eating Disorders, Neuropeptide Y, Peptide YY, Genetic association study
Disclosure: P. Shih, Nothing to Disclose; N. Schork, Nothing to Disclose; W. Berrettini, Nothing to Disclose; A. Bergen, Nothing to Disclose; P. Magistretti, Nothing to Disclose; C. Bloss, Nothing to Disclose; A. Van Zeeland, Nothing to Disclose; W. Kaye, Nothing to Disclose.

T138. The Sex Biased Phosphoproteome: A Novel Approach Towards Understanding The Molecular Basis for Sex Differences in Neuropsychiatric Diseases

Rita Valentino*, Debra Bangasser, Zach Plona, Hua Ding, Christopher McKennan, Steven Seeholzer

The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Background: Stress-related psychiatric disorders (e.g., depression, post-traumatic stress disorder) are nearly two fold more prevalent in females compared to males. Our recent studies implicated sex differences in signaling and trafficking of the receptor for corticotropin-releasing factor (CRF), the molecule that orchestrates the stress response, as a molecular mechanism for these differences. In females the CRF receptor (CRF1) was more highly coupled to its GTP-binding protein (Gs) and it did not associate with b-arrestin 2 following stress as seen in males. These sex differences rendered neurons of female rats more sensitive to CRF and less able to adapt to excess CRF through b-arrestin 2-mediated CRF1 internalization. In addition to promoting receptor internalization, b-arrestin 2 also acts as a scaffold linking receptors to G-protein independent signaling pathways. This suggests that CRF1 signaling is sex biased, such that in females signaling is preferentially through Gs-protein related pathways whereas in males it can involve b-arrestin 2-related, Gs-protein independent pathways. By engaging different signaling cascades stressors can have sex-specific cellular, physiological, behavioral and pathological consequences. Because Gs-protein and b-arrestin 2 signaling regulate phosphorylation dynamics in cells we tested the hypothesis that the excessive CRF that occurs in stress-related psychiatric disorders could result in sex specific phosphoprotein profiles. Keys to understanding sex differences in stress-related psychiatric disorders may lie in the differences between these profiles. This was tested by performing a deep phosphoproteomic analysis of cortex of male and female CRF overexpressing (CRF-OE) mice using stable isotope labeling of whole mouse (SILAM) and high resolution mass spectrometry.
Methods: : Experimental protocols were approved by IACUC of The Children's Hospital of Philadelphia and were in accordance with the NIH *Guide for the Care and Use of Laboratory Animals*. Male and female CRF-OE transgenic mice with the mMt-1 promoter driving the CRF gene (including introns) backcrossed onto the C57BL/6 mouse strain were purchased from Jackson Labs. Cortical protein

homogenates were obtained from experimental subjects and protein from male and female SILAM brains obtained from mice on a stable isotope labeled amino acid diet was added to experimental samples as an internal standard. After tryptic digest, phosphoproteins were enriched and separated by hydrophyllic interaction chromatography in conjunction with immobilized metal affinity chromatography. Samples were subjected to reversed phase LC-MSMS. Raw data were analyzed using MaxQuant 1.2.7.4 and Andromeda search engine.

Results: Over 5300 unique phosphopeptides were identified that were present in both female CRF-OE mice (FOE) and male CRF-OE mice (MOE). Approximately 14% of these differed between groups with 269 being more abundant in FOE and 131 being more abundant in MOE (1%FDR). Kinases were prominent in the FOE group (44 kinases) and were not as well represented in the MOE (10 kinases). Additionally, more phosphatases and phosphodiesterases were represented in the FOE compared to the MOE group. The different types of kinases in the two groups supported the concept that signaling was different between FOE and MOE mice. Calcium/calmodulin kinase (CAMK) subunits and serine/threonine kinases were prominent in the FOE group, whereas no specific kinase was more apparent in the MOE group. Analysis of the overrepresented amino acid motifs in both groups showed some overlap between the groups but also identified motifs that distinguished the groups. Finally, analysis of protein domains using PROSITE revealed that protein kinase domains dominated the FOE group and PDZ and Src domains were most representative in the MOE group. These initial findings support the hypothesis that sex biased CRF receptor signaling translates to different profiles of phosphoproteins in brain. Finally, an initial functional pathway analysis strongly implicated the FOE phosphoproteome in calcium signaling with >20 phosphoproteins related to this and also in Alzheimer's disease with key phosphoproteins related to amyloid b (A4) precursor protein binding and processing, including beta secretase and phosphorylation of tau, including tau tubulin kinase and CAMK.

Conclusions: Here we used a proteomic approach to test a hypothesis generated from receptor immunoprecipitation studies. A deep phosphoproteomic analysis comparing cortical tissue of male and female CRF-OE mice to mimic the CRF overactivity of stress-related psychiatric disorders revealed that a substantial proportion of the phosphoproteome differed significantly between the sexes. The different pattern of kinases and protein domains represented in the two groups supported the notion of sex biased CRF signaling. The finding that many phosphoproteins associated with Alzheimer's disease are exclusively present in the FOE phosphoproteome suggests a sex by stress interaction in this disease that may play a role in determining vulnerability.

Keywords: phosphoproteomic, sex differences, corticotropin-releasing factor, protein kinase, stress

Disclosure: R. Valentino, Nothing to Disclose; D. Bangasser, Nothing to Disclose; Z. Plona, Nothing to Disclose; H. Ding, Nothing to Disclose; C. McKennan, Nothing to Disclose; S. Seeholzer, Nothing to Disclose.

T139. Gamma Ventral Capsulotomy for Severe Obsessive-compulsive Disorder: A Double-blind, Randomized Controlled Trial

Euripedes Constantino. Miguel*, David Pauls, Benjamin Greenberg, Marcelo Hoexter, Marcelo Batistuzzo, André Gentil, Roseli G. Shavitt, Carlos A. Pereira, Juliana Belo. Diniz, Antonio C. Lopes, Georg Noren, Steven Rasmussen

Universidade de São Paulo, São Paulo, Brazil

Background: Lack of response to multiple treatments, including medications and behavior therapy, can be observed in up to 10 to 15% of obsessive-compulsive disorder (OCD) patients. For this subgroup, an ablative, Gamma Knife radiosurgical technique (Gamma ventral capsulotomy - GVC) is a treatment option. Preliminary findings suggest that this procedure is possibly efficacious and safe. However, double-blind, randomized controlled trials (DB-RCT) of ablative surgeries for any mental disorders were never done. The aim of this study was to conduct the first DB-RCT of Gamma ventral capsultomy for severe and untreatable OCD.

Methods: Sixteen untreatable DSM-IV OCD patients were selected. They were randomly assigned to active (Ata group, 8 patients) or "sham" treatment (ST group, 8 patients). Outcome raters were blind to patients' assignments. Blinding of study participants was accomplished by sedating all subjects throughout their procedures, and by coupling a false Gamma Knife chamber to the real Gamma Knife equipment. The surgical technique consisted of double-shot radiosurgical lesions at the anterior limb of the ventral internal capsule. Pre and post-operative follow-up assessments were provided, investigating OCD symptoms changes (with the Yale-Brown Obsessive-Compulsive Scale – YBOCS and with the Dimensional YBOCS – DYBOCS), depression/anxiety symptoms (with Beck Depression and Beck Anxiety inventories), global status, quality of life (with the Medical Outcomes Study SF-36), neuropsychological and personality changes. After 12 months of follow-up, blind was broken. ST group patients were then offered a true radiosurgery in an open study design (ATb group, 4 patients). Response criterion was defined by a minimum of 35% decrease in YBOCS scores, plus a "much improved", or "very much improved" ratings in the Clinical Global Impression (CGI) scale scores. To be accepted in the study, patients had to agree and sign an informed consent form, which was video recorded. A review panel confirmed every patient's adequacy for signing the consent form, inclusion, refractoriness and exclusion criteria.

Results: While in the blind phase, 3 of 8 patients randomized to the ATa group became responders at 12 months of follow-up. For the ST group, none of the 8 patients responded to treatment. Statistically significant differences at 12 months between the groups were observed in terms of YBOCS ($p = 0.046$) and DYBOCS total scores ($p = 0.016$) and impairment scores ($p = 0.021$). However, there were no differences in terms of depression/anxiety symptoms, or in different domains of the SF-36. By the last long-term follow-up visit (a mean of 54 months), 2 additional patients in ATa were responders. Two of 4 patients from the ATb responded after 12 months of follow-up. In conclusion, 7 of 12 patients (ATa plus ATb groups) responded to the radiosurgical treatment in the long term. Most adverse events were mild, including episodes of headache, nausea, paresthesia or pain at the insertion points of the stereotactic frame and weight changes. Two patients developed a manic episode after surgery. The most serious adverse event was an abnormal radionecrottic reaction in one patient, with brain edema, delirium and confabulation for a few days, and the late development of an asymptomatic radionecrotic cyst and transient memory deficits. Apart from this case, there were no adverse neuropsychological or personality changes.

Conclusions: This study is the first double-blind, placebo-controlled, randomized trial of an ablative surgery for the treatment of a psychiatric disorder. Active GVC is efficacious, when compared to a sham radiosurgical procedure. Its long-term efficacy profile is similar to other ablative (eg. capsulotomy, cingulotomy) or deep brain stimulation techniques, but craniotomy is never required. A severe side effect was observed in one patient. Consequently, this surgical procedure should be restricted to untreatable OCD cases in specialized research centers able to guarantee a very long follow-up for these patients until the long-term adverse effects of the procedure are clearly characterized.

Keywords: Neurosurgery, obsessive-compulsive disorder, anxiety disorders, randomized controlled trial,

Disclosure: E. Miguel, Nothing to Disclose; D. Pauls, Nothing to Disclose; B. Greenberg, Nothing to Disclose; M. Hoexter, Nothing to Disclose; M. Batistuzzo, Nothing to Disclose; A. Gentil, Nothing to Disclose; R. Shavitt, Nothing to Disclose; C. Pereira, Nothing to Disclose; J. Diniz, Nothing to Disclose; A. Lopes, Nothing to Disclose; G. Noren, Nothing to Disclose; S. Rasmussen, Nothing to Disclose.

T140. Resting Regional Cerebral Blood Flow to Predict Relapse in Cocaine Dependent Individuals

Hong Gu, Meredith J. McHugh, Yihong Yang, Conner Shope, Jacquelyn Braud, Michael D. Devous, Richard W. Briggs, N. Robrina Walker, C. Munro Cullum, Elliot A. Stein*, Bryon Adinoff

National Institute on Drug Abuse, National Institutes of Health, Baltimore, Maryland

Background: Cocaine addiction is a chronic and relapsing disorder characterized by the persistent use of cocaine in the face of negative outcomes. A failure to modify reward-driven behavior to avoid negative consequences is also seen in humans and animals with damage to the orbitofrontal cortex (OFC). Individuals addicted to cocaine exhibit reduced activity and blood flow in the OFC and poor performance in tasks sensitive to OFC functioning. However, it is unknown whether measures of OFC functioning can predict who relapses to cocaine use following a period of abstinence. In the current study we investigated whether tonic resting regional cerebral blood flow (rCBF) and neurocognitive measures sensitive to OFC functioning could predict relapse to cocaine use following a 2-4 week treatment episode.
Methods: 47 cocaine dependent individuals (43 males) at the end of a 2-4 week residential treatment episode and 22 healthy controls (15 males) completed 4 min resting perfusion fMRI scans using pseudo continuous arterial spin labeling (pCASL) to measure rCBF. During the same scan session participants completed a Stop Signal Task (SST). Within a week of this scan session all participants completed a series of neurocognitive measures sensitive to OFC functioning including the Wisconsin Card Sorting Task (WCST), the Balloon Analogue Risk Test (BART) and the Iowa Gambling Task (IGT). Cocaine-dependent participants were followed for 168 days post-treatment with weekly urine analysis and clinical interview to assess for relapse. Preprocessing and analyses were conducted in AFNI and involved motion correction, surround subtraction of sinc-interpolated control and tag images, spatial smoothing (FWHM = 6 mm), spatial normalization and non-linear implicit reference-based group-wise image registration. Group differences were assessed using linear mixed effects modeling and ANCOVAs controlling for gender as a covariate in these models. Prediction of relapse status at day 30 and day 168 was assessed using Cox and Logistic regression models.
Results: Individuals who relapsed by day 30 ($n = 22$) exhibited slower stop signal reaction time (SSRT) and more perseverative responses on the WCST relative to healthy controls. The only difference observed between individuals who relapsed at day 30 and those who did not was a marginally slower SSRT among the former. No other behavioral differences were observed. Relapse by day 30 was also associated with reduced rCBF in the left and right medial OFC and enhanced rCBF in the left parahippocampal gyrus relative to healthy controls. Together, enhanced rCBF to the left medial OFC and the left parahippocampal gyrus correctly classified 77.8% of cocaine-users as relapsers or non-relapsers at day 30. Including SSRT in this model did not improve relapse status classification. Resting CBF in the left parahippocampal gyrus also predicted time to relapse up to 24 weeks post-treatment. Importantly, clinical characteristics such as cocaine craving, obsessive-compulsive cocaine use and cocaine use history were not related to relapse risk in the current sample.
Conclusions: Previous studies have demonstrated reduced rCBF in the OFC among cocaine-dependent individuals using SPECT. The current study extends upon these findings, showing that greater reductions in rCBF to the medial OFC are associated with enhanced risk of early relapse. Relapse by day 30 was also associated with greater perseverative responding and poorer response inhibition relative to healthy controls. However, the strongest predictor of relapse at day 30 and time to relapse up to 24 weeks post-treatment was enhanced rCBF in the left parahippocampal gyrus. While unexpected, abnormal activation and rCBF to this region has been observed in a number of previous studies as a function of cocaine-dependence and abuse history and has previously been associated with treatment retention and age of cocaine-use onset. Future studies that aim to clarify the mechanism linking enhanced rCBF to the parahippocampal gyrus and relapse risk may prove beneficial to the identification of new therapeutic targets.
Keywords: cerebral blood flow, cocaine addiction, relapse, orbitofrontal, parahippocampal gyrus
Disclosure: H. Gu, Nothing to Disclose; M. McHugh, Nothing to Disclose; Y. Yang, Nothing to Disclose; C. Shope, Nothing to Disclose; J. Braud, Nothing to Disclose; M. Devous, Nothing to Disclose; R. Briggs, Nothing to Disclose; N. Walker, Nothing to Disclose; C. Cullum, Nothing to Disclose; E. Stein, Nothing to Disclose; B. Adinoff, Nothing to Disclose.

T141. Polygenic Variation across the Folate Metabolic Pathway Influences Frontal Cortical Thickness: Implications for Altered Neurodevelopment in Schizophrenia

Joshua L. Roffman*, Noah J. Silverstein, Avram J. Holmes, Phil H. Lee, Marisa O. Hollinshead, Jordan W. Smoller, Randy L. Buckner

Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts

Background: Folic acid plays a critical role in methylation reactions that govern normal brain development and function. Reduced folate levels and hypofunctional genetic variants in the folate metabolic pathway have been associated with several neurodevelopmental disorders including schizophrenia. Two recent clinical trials indicate a benefit of folate supplementation in schizophrenia, but only among patients with certain functional genetic variants in the folate metabolic pathway. A small number of these variants have also been shown to affect *in vivo* brain imaging phenotypes in health and schizophrenia, but a comprehensive evaluation of genetic variation across the folate pathway has not been attempted. The present investigation employed a large data set of *in vivo* brain imaging and genetic data obtained from healthy individuals (the Brain Genomics Superstruct project). Using genome-wide data, we explored the net effect of genetic variation across the entire folate metabolic pathway on gray matter thickness of the prefrontal cortex, a strongly heritable measure that is consistently reduced in chronic and first episode schizophrenia patients, and that also shows reductions in unaffected relatives and other high-risk groups.
Methods: We studied 441 individuals of European ancestry, split evenly into demographically matched discovery and replication samples, using standardized structural MRI sequences on identical 3T Siemens Trio magnets. Left prefrontal cortical thickness was extracted using FreeSurfer. Using the Gene Ontology database, we identified 33 folate-related genes, and examined genotypes for 806 associated SNPs obtained using the Illumina Omni1Quad microarray. Within the discovery sample (Set 1, n = 221), we identified lists of SNPs associated with prefrontal cortical thickness at different thresholds of significance ($p_{(t)} = .5, .4, .3, .2, .1$) along with their effect sizes. Using Plink, these SNPs were incorporated into polygene score models that were then tested in the replication set (Set 2, n = 220), to determine the relationship between polygene score and prefrontal cortical thickness. The same process was used to derive polygene scores in Set 2 and apply them to prefrontal cortical thickness in Set 1. All analyses included population stratification measures, collection site, age, and gender as covariates.
Results: Polygene scores for prefrontal cortical thickness that were derived from Set 1 significantly ($p < .05$) predicted cortical thickness in Set 2, at each $p_{(t)}$ threshold. Similarly, polygene scores that were derived from Set 2 also significantly predicted cortical thickness in Set 1. Random polygene scores were also derived in each set, using 806 SNPs that were randomly generated from the genome-wide data set. These randomly-derived scores showed no relationship to prefrontal cortical thickness, and accounted for significantly less variance in cortical thickness than did the folate gene-derived scores.

Conclusions: Genetic variation across the folate metabolic pathway contributes significantly to variation in prefrontal cortical thickness, a brain phenotype relevant to altered neurodevelopment in schizophrenia. Interactive effects of folate genes and nutritional folate intake on biochemical measures such as DNA methylation and homocysteine metabolism have been well described. The present findings motivate additional efforts to examine interactive effects of dietary folate and folate-related genes on normal brain structure and function, and to determine whether folate levels during neurodevelopment interact with genetic load to influence schizophrenia risk.
Keywords: folate, genetics, structural MRI, schizophrenia, cortical thickness
Disclosure: J. Roffman, **Part 4:** Dr. Roffman receives grant support from PamLab, and participated in the Harvard-MIT Divison of Health Sciences and Technology Clinical Investigator Training Program, which was supported through undrestricted educational grants from Merck and Pfizer; N. Silverstein, Nothing to Disclose; A. Holmes, Nothing to Disclose; P. Lee, Nothing to Disclose; M. Hollinshead, Nothing to Disclose; J. Smoller, Nothing to Disclose; R. Buckner, Nothing to Disclose.

T142. Convergence of Two Key Pathways of Schizophrenia: DISC1-serine Racemase Interaction in Astrocytes
Mikhail V. Pletnikov*, Martin Ma, Sofya Abazyan, Bagrat Abazyan, Akira Sawa, Solomon H. Snyder

Johns Hopkins University School of Medicine, Baltimore, Maryland

Background: Genetic polymorphism and pathogenic mutations of Disrupted-In-Schizophrenia-1 (DISC1) and D-serine/NMDA receptor hypofunction have both been linked to schizophrenia. Recent reports have identified expression of DISC1 in astrocytes that are the main source of D-serine in the brain. Thus, we explored a putative role for DISC1 in D-serine metabolism in astrocytes.
Methods: We studied interaction between DISC1 and serine racemase (SR), the enzyme that coverts L-serine to D-serine. In addition, the effects of mutant DISC1 on D-serine production were evaluated in primary astrocytes and brain tissue derived from transgenic mice that selectively express mutant DISC1 in astrocytes. Glutamate uptake and expression of the major astrocytic markers were also measured in the same samples. In a series of behavioral tests, we assessed schizophrenia-related behavioral alterations and ameliorative effects of D-serine treatments in GFAP-mutant DISC1 mice.
Results: We found that DISC1 binds to and stabilizes SR. Pathogenic disruption of this interaction by mutant DISC1 leads to accelerated ubiquitination of SR and decreased D-serine production. These changes were further confirmed in brain samples from transgenic mice with astrocytic expression of mutant DISC1. In contrast, mutant DISC1 does not change levels of ALDH1L1, connexins, GLT-1 or binding partners of DISC1 and SR, LIS1 or PICK1. Consistently with our biochemical findings, transgenic mice display greater responses to an NMDA antagonist, MK-801, in open field and pre-pulse inhibition of the acoustic startle tests and are more sensitive to the ameliorative effects of D-serine.
Conclusions: Our study indicates that DISC1 plays an important role in regulation of D-serine production in astrocytes and for the first time links DISC1 and NMDA pathophysiological mechanisms of schizophrenia.
Keywords: DISC1, serine racemase, D-serine, astrocytes, schizophrenia
Disclosure: M. Pletnikov, Nothing to Disclose; M. Ma, Nothing to Disclose; S. Abazyan, Nothing to Disclose; B. Abazyan, Nothing to Disclose; A. Sawa, **Part 1:** Pfizer, Sanofi-Aventis, Eli Lilly, Takeda, Astellas, Tanabe-Mitsubishi, Dainippon-sumitomo, Amgen, Taisho, Asubio, Otsuka, **Part 3:** Pfizer, Sanofi-Aventis, Eli Lilly, Takeda, Astellas, Tanabe-Mitsubishi, Dainippon-sumitomo, Amgen, Taisho, Asubio, Otsuka, **Part 4:** Johnson and Johnson; S. Snyder, Nothing to Disclose.

T143. Effects of Two-week Chronic Treatment with Phendimetrazine or Its Primary Active Metabolite, Phenmetrazine, on Choice between Cocaine and Food in Rhesus Monkeys
Matthew L. Banks*, Bruce Blough, Steve Negus

Virginia Commonwealth University, Richmond, Virginia

Background: There is currently no Food and Drug Administration-approved pharmacotherapy for the treatment of cocaine dependence. We have previously shown that continuous 7-day treatment with the dopamine/norepinephrine vs. serotonin-selective monoamine releaser phenmetrazine decreased cocaine self-administration under several schedules of reinforcement, including a concurrent cocaine vs. food choice procedure. However, the clinical utility of phenmetrazine as a candidate medication is limited by its high abuse potential. Phendimetrazine is a clinically available Schedule III stimulant that functions as a prodrug for phenmetrazine and may have lower abuse liability than phenmetrazine. The goal of this study was to compare effects of continuous 14-day treatment with phendimetrazine and phenmetrazine on cocaine vs. food choice in rhesus monkeys. We hypothesized that phendimetrazine and phenmetrazine would produce similar decreases in cocaine choice.
Methods: Four rhesus monkeys, implanted with a chronic indwelling double-lumen venous catheter, initially responded during daily 2-hr sessions under a concurrent schedule of food delivery (1-g pellets, fixed-ratio 100 schedule) and cocaine injections (0–0.1 mg/kg/injection, fixed-ratio 10 schedule). One lumen of the double-lumen catheter was designated as the "cocaine" lumen and was always filled with the self-administered cocaine solution. The other lumen was designated as the "treatment" lumen, and saline, (+)-phendimetrazine (0.32–1.0 mg/kg/hr), or (+)-phenmetrazine (0.1–0.32 mg/kg/hr) was continuously infused 23 hrs/day during 14-day treatment blocks. Treatment blocks with phenmetrazine or phendimetrazine were counter-balanced both within a test compound dose and across test compounds. All doses of phenmetrazine or phendimetrazine were tested in a given monkey before initiating treatment blocks with the other compound. Treatment blocks with phenmetrazine or phendimetrazine were followed by saline treatment conditions for at least 5 days and until the cocaine choice dose-effect function returned to pre-test levels. All studies were approved by the Virginia Commonwealth University IACUC and were conducted in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*.
Results: Under saline treatment conditions, food was primarily chosen during availability of low cocaine doses (0, 0.0032, and 0.01 mg/kg/injection), and cocaine was primarily chosen during availability of higher cocaine doses (0.032 and 0.1 mg/kg/inj). There was no significant effect of either phenmetrazine or phendimetrazine treatment on cocaine choice after 7 days. After 14 days of treatment with the highest doses of phenmetrazine (0.32 mg/kg/hr) or phendimetrazine (1.0 mg/kg/hr), there was a small, but significant, rightward shift in the cocaine choice dose-effect function such that choice of 0.032 mg/kg/injection cocaine was significantly decreased by approximately 50%. Furthermore, individual differences in treatment effects were noted. For example, phenmetrazine produced at least a 0.5 log unit rightward shift in the cocaine choice dose-effect function in 1 out of 4 monkeys; whereas, phendimetrazine produced at least a 0.5 log unit rightward shift in the cocaine choice dose-effect function in 2 out of 4 monkeys. Moreover, rightward shifts in the cocaine dose-effect function were still apparent one and three days after termination of phenmetrazine (0.32 mg/kg/hr) and phendimetrazine (1.0 mg/kg/hr) treatment, respectively. Phenmetrazine did not significantly alter rates of operant behavior over the 14-day treatment period. In contrast, phendimetrazine (1.0 mg/kg/hr) treatment significantly decreased rates of operant behavior during the first seven days of treatment, and tolerance developed to this effect of phendimetrazine such that rates of operant behavior were not significantly different from saline treatment conditions at the end of the 14-day treatment period.

Conclusions: Overall, these results show that phendimetrazine, like its active metabolite phenmetrazine, can produce significant though modest decreases in cocaine choice in rhesus monkeys. Phendimetrazine may be especially suitable as a candidate agonist medication for human laboratory and clinical studies because it is clinically available as a Schedule III drug.
Keywords: Cocaine; choice; monkey; agonist medication; monoamine releaser
Disclosure: M. Banks, **Part 4:** Dr. Banks declares that during the past two years, he has received compensation as a collaborator with the pharmaceutical companies Abbott and Purdue for research grant projects related to opioid pharmacology and analgesic drug development. The present study was not related to this professional relationship; B. Blough, Nothing to Disclose; S. Negus, **Part 4:** Dr. Negus declares that during the past three years, he has received compensation as a consultant for or collaborator with the pharmaceutical companies Abbott, Alkermes, Argolyn, Grunenthal, and Limerick Biopharma for projects related to opioid pharmacology, analgesic drug development or assessment of abuse liability. The present study was not related to any of these professional relationships.

T144. Altered Functional and Structural Brain Connectivity in First-episode Psychosis

Tom A. Hummer*, John D. West, Yang Wang, Nikki Mehdiyoun, Jenifer L. Vohs, Michael M. Francis, Emily Liffick, Brenna C. McDonald, Andrew J. Saykin, Alan Breier

Indiana University School of Medicine, Indianapolis, Indiana

Background: Schizophrenia has been hypothesized to be a disorder of altered cortical connectivity. However, a detailed understanding of the circuits that may account for this illness is unclear. A potentially powerful approach to elucidating cortical networks is the combination of different yet complementary imaging modalities. Functional magnetic resonance imaging (fMRI) provides information about brain activity in cerebral regions of interest, and diffusion tensor imaging (DTI) measures the integrity of white matter tracts that connect cerebral areas. Together, fMRI and DTI provide a synergistic approach to assessing the functional integrity of cortical circuits. First-episode psychosis (FEP) is an optimal condition in which to study the pathophysiology of schizophrenia, because it is associated with fewer potential confounds (such has prolonged medication exposure and chronicity). In this study, we conducted an integrative neuroimaging investigation to identify alterations in functional and structural brain connectivity in FEP by combining resting-state fMRI and DTI.
Methods: Twenty-three patients (mean age 22.4, sd = 3.5; 18 M, 5 F) with a DSM-IV-TR diagnosis of a psychotic disorder (excluding primary mood and substance-induced psychoses) took part in this study. Patients were within the first 5 years of the onset of psychotic symptoms (mean 12.4 months since onset of treatment). Twelve healthy, age-, gender-, and parental SES-matched subjects (mean age = 24.1; sd = 3.6; 8 M, 4 F) comprised the control group. Imaging studies were conducted on a 3T Siemens Tim Trio MRI scanner. In addition to a standard structural scan, methods for characterizing default mode network (DMN) functional connectivity, via resting-state fMRI, and structural white matter connectivity, via DTI, were conducted. *Resting State fMRI*: This paradigm is utilized to examine "default mode" connectivity of the brain in the absence of a specific task and is thought to reflect general awareness and integrity of inter-regional communication. Participants were instructed to close their eyes and try not to think of anything in particular during the 6-minute fMRI scan. The fMRI time-series underwent standard preprocessing and was temporally filtered to focus on low-frequency activity (0.01-0.1 Hz). An independent components analysis (ICA) established z-scores that defined the strength of a DMN component in each voxel. A DMN mask for the entire sample was defined as those voxels with DMN component z-scores significantly different from zero ($p < .001$, FDR corrected). *DTI*: To examine differences in structural connectivity between groups, we investigated group differences in fractional anisotropy (FA), a marker of white matter organization and maturity. DTI images were corrected for motion and eddy artifacts. Using tract-based spatial statistics (TBSS), individual FA maps were nonlinearly registered to a standard template and affine-transformed into MNI space. Each participant's FA image was then projected onto a mean FA skeleton, resulting in individual skeletonized FA maps. The mean FA skeleton (thresholded at mean FA > 0.2) was then used as a mask for voxel-wise group ANCOVA, controlling for age and sex (uncorrected $p < .01$; voxel count $k > 20$).
Results: Frontal regions showed significantly altered DMN connectivity between controls and patients ($p < .01$, cluster size $k > 50$ voxels). Patients had greater positive connectivity in left medial prefrontal cortex ($k = 117$ voxels) and less negative connectivity in right inferior frontal cortex ($k = 54$). Furthermore, exploratory analyses revealed a significant correlation between default mode activity in the left inferior frontal cluster and patients' PANSS Marder Cognition/Disorganized Thought subscale score ($r = .49$, $p = .03$), indicating that abnormal activity in this cluster was related to symptom severity. For DTI, patients had reduced FA compared to controls in left superior longitudinal fasciculus ($k = 37$ voxels). By contrast, patients had greater FA than controls in the right posterior inferior fronto-occipital fasciculus ($k = 31$). In addition, multiple tracts demonstrated a significant interaction between group and age. In these regions, FA in controls was more positively associated with age than FA in patients was, which included three clusters in left superior/anterior corona radiata ($k = 60$; $k = 26$; $k = 22$), right anterior inferior fronto-occipital fasciculus ($k = 50$), left anterior thalamic radiation ($k = 29$), left superior longitudinal fasciculus ($k = 22$), and left corticospinal tract ($k = 22$).
Conclusions: These results contribute to the growing evidence that neural connectivity is altered in FEP, particularly in inferior frontal cortical regions. This altered connectivity, particularly between frontal and temporal or parietal cortices may be a significant driver in the development of disordered thoughts and psychotic episodes. Longitudinal follow-up will be necessary to test this hypothesis. Convergent imaging data can provide insight into what neural alterations in psychosis and elucidate mechanisms to facilitate development of early interventions.
Keywords: schizophrenia, psychosis, default mode, resting state fMRI, diffusion tensor imaging
Disclosure: T. Hummer, Nothing to Disclose; J. West, Nothing to Disclose; Y. Wang, Nothing to Disclose; N. Mehdiyoun, Nothing to Disclose; J. Vohs, Nothing to Disclose; M. Francis, Nothing to Disclose; E. Liffick, Nothing to Disclose; B. McDonald, Nothing to Disclose; A. Saykin, Nothing to Disclose; A. Breier, Nothing to Disclose.

T145. Monoamine Oxidase A in Subtypes of Depression: A [C-11] Harmine Positron Emission Tomography Study

Lina Chiuccariello*, Sylvain Houle, Laura Miler, Robert G. Cooke, Robert D. Levitan, Stephen J. Kish, Alan A. Wilson, Pablo Rusjan, Jeffrey H. Meyer

Centre for Addiction and Mental Health/University of Toronto, Toronto, Ontario, Canada

Background: Major depressive disorder (MDD) is the leading cause of death in mid to high income countries and the leading cause of years lost to disability worldwide. A key reason for the burden of this illness is treatment resistance. One approach to overcoming treatment resistance is to identify pathological subtypes of illness so as to better match treatment to illness. Monoamine oxidase A (MAO-A) total distribution volume (V_T), an index of MAO-A density, has been shown to be robustly increased in a number of brain regions, particularly the prefrontal and anterior cingulate cortices, during major depressive episodes (MDE) in two positron emission tomography neuroimaging studies. This finding was further replicated in postmortem brain, showing a similar and significant increase in MAO-A protein levels in the prefrontal cortex. However, the subtypes of depression for which MAO-A levels in the brain are most elevatedis unknown. We

hypothesized that MAO-A V_T in the prefrontal and anterior cingulate cortices willbe increased in MDE with a high severity of symptoms and MDE with atypical symptoms. The rationale for predicting that MAO-A V_T would be elevated in severe MDE was that a retrospective data review in the first positive neuroimaging study, found that more severe MDE, as defined by a Hamilton Rating Scale for Depression (HRSD) score of greater or equal to 20, was associated with higher MAO-A V_T in the prefrontal and anterior cingulate cortices. The rationale for predicting elevated MAO-A V_T in MDE with atypical symptoms was that this subtype preferentially responds to MAO inhibitors, hence, it is possible that the atypical MDE subtype expresses a greater level of the MAO-A target.
Methods: MAO-A total distribution volume (MAO-A V_T), an index of MAO-A density, was measured using [^{11}C]harmine PET in subjects with MDE secondary to MDD ($n = 42$) and healthy controls ($n = 35$). The effect of severity of symptoms and symptom type (atypicality) were analyzed using a multivariate analysis of variance (MANOVA), with prefrontal cortex (PFC) and anterior cingulate cortex (ACC) MAO-A V_T as the dependent variables and severity and atypicality as the independent variables. As a secondary analysis, a MANOVA was used to test the effects of severity and atypicality on all regions sampled (including caudate, putamen, thalamus, midbrain, hippocampus and temporal cortex).
Results: MAO-A V_T was elevated in severe and atypical-type depression ($F_{(2,37)} = 7.59$, $p = 0.002$ and $F_{(2,37)} = 5.83$, $p = 0.006$, respectively) compared to individuals without these symptoms in the prefrontal and anterior cingulate cortices. MAO-A V_T was also elevated in all other brain regions sampled in severe and atypical-type depressed individuals ($F_{(8,31)} = 2.69$, $p = 0.023$ and $F_{(8,31)} = 2.62$, $p = 0.026$, respectively).
Conclusions: The two factors of severity and atypicality are highly predictive of elevated MAO-A V_T in the prefrontal and anterior cingulate cortices, as well as the other brain regions sampled. These findings argue for a personalized treatment approach in the future development of MAO-A inhibitors in which severity and atypicality are targeted. More specifically, we suggest that severity (as defined by a cutoff score similar to a HDRS of greater than 20) and atypicality (as defined by presence of hypersomnia and either hyperphagia or weight gain) should be investigated as predictors of response to treatment with MAOIs, particularly selective MAO-A inhibitors. This perspective is based upon the implication that greater expression of target should be associated with greater likelihood of response to therapeutics for that target. Our findings are consistent with a recent report of a preferential response to MAO-A inhibitor treatment in severe MDE, and past reports of preferential response of atypical MDE to MAO inhibitors.
Keywords: Depression, MAO-A, Positron Emission Tomography, severity, atypical
Disclosure: L. Chiuccariello, Nothing to Disclose; S. Houle, **Part 1:** Eli Lilly, Bristol-Myers Squibb and SK Life Sciences; L. Miler, Nothing to Disclose; R. Cooke, Nothing to Disclose; R. Levitan, Nothing to Disclose; S. Kish, Nothing to Disclose; A. Wilson, Nothing to Disclose; P. Rusjan, Nothing to Disclose; J. Meyer, **Part 1:** Sk Life Sciences, Eli Lilly, Lundbeck, Takeda, Bristol-Myers Squibb, Mylan, **Part 4:** Lundbeck.

T146. Increased Expression of Neurokinin-1 Receptors in the Central Nucleus of the Amygdala Mediates Escalated Alcohol Self-administration and Increased Potency of Neurokinin-1 Receptor Antagonism in Alcohol Preferring P Rats

Jesse R. Schank*, Hui Sun, Courtney King, Jenica Tapocik, Estelle Barbier, Kejun Cheng, Kenner Rice, Markus Heilig

National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland

Background: We have previously demonstrated that genetic deletion or pharmacological blockade of the neurokinin-1 receptor (NK1R) decreases alcohol intake, alcohol reward, and stress-induced reinstatement of alcohol seeking. Furthermore, NK1R antagonism suppresses escalated alcohol self-administration in alcohol preferring P rats. The latter effect is associated with increased mRNA for the *TacR1* gene, which encodes the NK1R, and increased NK1R receptor binding in the central nucleus of the amygdala (CeA) of P rats relative to Wistar controls. The experiments outlined below further explore the pharmacogenetic interaction that influences the potency of NK1R antagonism in P rats.
Methods: First, we trained male P rats to self-administer 10% ethanol on a fixed-ratio 3 schedule and implanted cannulae directed at the CeA or prefrontal cortex (PFC). After responding stabilized, the NK1R antagonist L822429 (0 or 7.5 μg) was infused 10 minutes prior to the session on the following day and alcohol self-administration rates were measured. Next, we sequenced 2 kb upstream of the transcriptional start site (TSS) of the rat *TacR1* gene to determine if polymorphisms are present in the P rat that might contribute to increased expression of the receptor. Polymorphisms identified in the promoter region were further analyzed by electromobility shift assay (EMSA) to determine transcription factor binding potential.
Results: Intra-CeA infusion of L822429 decreased alcohol self-administration rates in P rats, replicating the systemic effects observed in previous experiments. However, infusion into the PFC had no effect on self-administration behavior. Sequencing of the *TacR1* promoter identified a single nucleotide polymorphism (G-C) at position -1372 from the TSS. Genotyping analysis revealed that all P rats, but only 18% of their founder Wistar population, were CC homozygous. EMSA showed increased transcription factor binding to probes containing cytosine at this location, consistent with an increase of *TacR1* expression in P rats. This effect was observed in nuclear extracts from amygdala tissue, but not striatal tissue.
Conclusions: Collectively, these results support the notion that genetic variation of the *TacR1* locus can contribute to high rates of alcohol self-administration, while at the same time increasing sensitivity to NK1R antagonist treatment. This is possibly mediated by differences in transcription factor binding to the *TacR1* promoter in a regionally specific manner.
Keywords: Substance P Pharmacogenetic Interaction Alcohol Reinforcement
Disclosure: J. Schank, Nothing to Disclose; H. Sun, Nothing to Disclose; C. King, Nothing to Disclose; J. Tapocik, Nothing to Disclose; E. Barbier, Nothing to Disclose; K. Cheng, Nothing to Disclose; K. Rice, Nothing to Disclose; M. Heilig, Nothing to Disclose.

T147. Major Depressive Disorder is Associated with Abnormal Responses in the Dorsal Mid-insula during Attention to Interoceptive States

William K. Simmons*, Jason Avery, Joel Barcalow, Scott Mosemann, Jerzy Bodurka, Wayne C. Drevets

Laureate Institute for Brain Research, Tulsa, Oklahoma

Background: Somatic complaints and aberrant interoceptive awareness are common features in the clinical presentation of major depressive disorder (MDD). Recently, neuroscientific evidence has accumulated demonstrating that the mid-insula is a primary cortical structure underlying interoceptive awareness (Simmons, Avery, Barcalow, et al., In Press, *Human Brain Mapping*). In the present study we sought to assess whether MDD and depression severity are associated with abnormal activity and functional connectivity within interoceptive insular cortex.
Methods: We recruited from the community 20 unmedicated adults with MDD in a current depressive episode and 20 healthy control participants. All participants underwent functional Magnetic Resonance Imaging (fMRI) while performing a task involving interoceptive attention to heart, stomach, and bladder sensations. During 'interoception trials' subjects saw either the word "heart" "stomach" or "bladder" for 10 seconds, during which time they focused attention on their heart, stomach, or bladder sensations. In addition, subjects also underwent a separate resting-state scan. Echoplanar imaging was conducted with a

3T MRI scanner and a 32-element array of receive-only head surface coils which granted superior image quality at high spatial resolution. We performed the following four statistical analyses: (1) A between-groups comparison of activity in the dorsal mid-insula during interoceptive attention tasks, (2) an assessment of the relationship between dorsal mid-insula activity and depression severity, (3) between-groups comparisons of resting-state functional connectivity to dorsal mid-insula, and (4) an assessment of the relationship between interoceptive insula functional connectivity and depression severity.

Results: Relative to the healthy controls, the unmedicated MDD subjects exhibited reliably less activity bilaterally in the dorsal mid-insula during interoception, and the magnitude of the response to the interoception task in this region was negatively correlated with depression severity. Interestingly, the group differences in insula activity were observed during attention to signals across multiple interoceptive modalities (e.g., attention to heartbeat, stomach, and bladder sensation). MDD was also associated with greater resting-state functional connectivity between the dorsal mid-insula and brain regions implicated previously in MDD, including the amygdala, subgenual prefrontal cortex, and orbitofrontal cortex. In addition, functional connectivity among these regions and the interoceptive insula was positively correlated with depression severity.

Conclusions: These results support accounts that MDD is associated with abnormal interoceptive representation within the insula. Our findings demonstrate that these interoceptive abnormalities affect awareness of interoceptive signals broadly (e.g., attention to heartbeat, stomach, and bladder signals), rather than within a single interoceptive channel (e.g., heartbeat signals alone). The findings of the present study establish the dorsal mid-insula as an important region within the neurocircuitry underlying MDD, and demonstrate that abnormal activity and connectivity within the interoceptive mid-insula plays an important role in the altered somatic awareness experienced by many patients with MDD, and may offer a promising therapeutic target for depression treatments.

Keywords: Depression, Interoception, Insula, Interoception, Functional Connectivity

Disclosure: W. Simmons, Nothing to Disclose; J. Avery, Nothing to Disclose; J. Barcalow, Nothing to Disclose; S. Mosemann, Nothing to Disclose; J. Bodurka, Nothing to Disclose; W. Drevets, **Part 1:** Wayne Drevets has received consulting fees for Johnson & Johnson, Inc., Esai Inc., and Myriad/ Rules Based Medicine, Inc., **Part 2:** Wayne Drevets received more than $10,000 from has been Johnson & Johnson, Inc.

T148. Smooth Pursuit Eye Movement, Prepulse Inhibition, and Auditory Paired Stimuli Processing Endophenotypes across the Schizophrenia - Bipolar Disorder

Elena I. Ivleva*, Amanda F. Moates, Jordan Hamm, Ira Bernstein, Darwynn Cole, Brett Clementz, Gunvant Thaker, Carol A. Tamminga

UT Southwestern Medical Center, Dallas, Texas

Background: Accumulating evidence indicates that dimensional characterization of psychosis captures an important aspect of the manifestation of severe mental illness. Optimal methods for categorizing psychotic illnesses [e.g., schizophrenia (SZ) and bipolar disorder (BD)] remain uncertain given the lack of biology-based diagnostic criteria. A promising strategy that seeks to identify valid diagnostic markers is the study of endophenotypes: the heritable characteristics of brain structure/function that are theoretically interposed between genes and behavior and may provide more efficient routes to discovery of molecular underpinnings of disease definition than clinical syndromes. In this study we examined 3 neurophysiological paradigms (smooth pursuit eye movement (SPEM), prepulse inhibition (PPI) and auditory event related potentials (ERP) in a paired stimuli task) as putative psychosis endophenotypes, hypothesizing common alterations across the schizophrenia SZ-BD psychosis dimension.

Methods: Sixty four SZ probands (SZP), 40 psychotic BD, type I, probands (BDP), 31 relatives of SZP (SZR), 26 relatives of BDP (BDR), and 53 controls (HC) were tested. Standard clinical characterization, as well as SPEM (Ramp-Mask-Ramp task), PPI (primary outcome at 120 ms interstimulus interval), and auditory paired stimuli paradigm with ERP frequency domain measures were administered. The primary analyses were carried out using logistic regression with the effect sizes described in terms of the logistic regression parameter estimates.

Results: There were no differences between either SZP and BDP or SZR and BDR on any of the SPEM, PPI or ERP measures (all $p > .25$). Compared to HC, SZP and BDP had lower SPEM maintenance ($p < .05$) and predictive pursuit ($p < .001$) gain, and ERP theta/alpha ($p < .02$) and beta magnitudes ($p < .02$) to the initial stimulus. PPI did not differ between the psychosis probands and HC (PPI = 44-47% and 50% in probands and HC, respectively; $p > .51$). Compared to HC, SZR and BDR had lower predictive pursuit gain at higher velocities (18.7 and 25.0°/sec; $p < .03$), as well as ERP theta/alpha and beta magnitudes to the first stimulus with differences ranging from significant to a trend level ($p = .03$-$.11$). Neither active symptoms severity, nor concomitant medications were associated with neurophysiological outcomes. SPEM, PPI and ERP scores had low inter-correlations ($r = .03$-$.46$).

Conclusions: These findings support SPEM predictive pursuit and lower frequency auditory ERP activity in a paired stimuli paradigm as putative endophenotypes of psychosis common to SZ and BD probands and relatives. PPI did not differ between the psychosis probands and HC primarily due to lower PPI in HC. Neither active symptoms severity nor concomitant treatments had an effect on SPEM, PPI or ERP, supporting these measures as 'trait' biological markers. SPEM, PPI/PPF, and ERP were found to be independent measures, possibly mediated by divergent biological circuitries. Future research examining heritability and molecular underpinnings of the psychosis endophenotypes may further understanding of the biology-driven mechanisms of psychosis and aid in the development of biology-based diagnostic definitions and novel treatments.

Keywords: psychosis; schizophrenia; bipolar disorder; smooth pursuit eye movement, PPI, auditory ERP

Disclosure: E. Ivleva, Nothing to Disclose; A. Moates, Nothing to Disclose; J. Hamm, Nothing to Disclose; I. Bernstein, Nothing to Disclose; D. Cole, Nothing to Disclose; B. Clementz, Nothing to Disclose; G. Thaker, Nothing to Disclose; C. Tamminga, Nothing to Disclose.

T149. Adjunctive Topiramate in Patients with Schizophrenia-spectrum Disorders: Results from a Meta-analysis of 9 Randomized Controlled Trials

Christoph U. Correll*, Lawrence Maayan, Marc De Hert, Dan Cohen

Albert Einstein College of Medicine; Hofstra North Shore LIJ School of Medicine, Glen Oaks, New York

Background: Despite pharmacologic advances, still too many patients with schizophrenia are treatment resistant to available antipsychotic medications. Although a number of augmentation options have been studied, no such strategy has a sufficiently strong evidence base to warrant regulatory approval. Recently, a number of studies utilized topiramate as an adjunctive agent to achieve weight loss in antipsychotic treated patients with schizophrenia. In addition, a significant number of these studies also targeted psychopathology. However, no formal meta-analysis has been conducted to synthesize the results and investigate moderators and mediators of treatment outcomes.

Methods: We conducted a systematic literature search in PubMed and Google Scholar from database inception until May 6, 2012, using the following key words: "random*" AND "topiramate" AND "antipsych*" OR "neurolept*" OR specific names of antipsychotics. We further hand-searched reference lists for additional studies and contacted authors for unpublished data. Included were randomized trials comparing adjunctive topiramate to placebo or open antipsychotic treatment in schizophrenia-spectrum disorder patients. Two indepen-

dent evaluators extracted data. Standardized and weighted mean difference (SMD/WMD), risk ratio (RR), and number-needed-to-harm (NNH) ± 95% confidence intervals (CI) were calculated.
Results: In 9 RCTs, lasting 14.1 ± 6.2 weeks, 452 patients (38.0 ± 5.3 years, 57.4% male, 94.9% with schizophrenia-spectrum disorders) were randomized to topiramate (100-400 mg/day) vs. placebo (N = 8) or open antipsychotic treatment (N = 1). Topiramate outperformed the comparator regarding change/endpoint in Positive and Negative Syndrome Scale (PANSS)/Brief Psychiatric Rating Scale (BPRS) total score (N = 5, n = 269, SMD:-0.55(95%CI:-0.98,-0.13), p = 0.01) PANSS positive symptoms (N = 4, n = 190, SMD:-0.55(95%CI:-1.0,-0.11), p = 0.01), negative symptoms (N = 4, n = 190, SMD:- 0.62(95%CI:-1.13,-0.10), p = 0.02; I2 = 64%) and general psychopathology (N = 3, n = 179, SMD:-0.69(95%CI:-1.27,-0.11), p = 0.02). Furthermore, topiramate outperformed the comparator regarding body weight (N = 8, n = 390, WMD:–3.21 kg(95%CI:-5.46,-0.69), p = 0.0005; I2 = 84%) and body mass index (BMI) (N = 5, n = 218, WMD:–1.77(95%CI:-2. 75,-0.79), p = 0.0004; I2 = 75%). Clozapine treatment mediated both greater efficacy and lesser weight loss associated with topiramate, while neither outcome was affected by topiramate dose, study duration, or inpatient status. All-cause discontinuation was similar between topiramate and the control group (RR:1.13 (95%CI:0.53,2.42), p = 0.74). Topiramate caused more paraesthesia than placebo (RR:2.89, CI:1.38,6.07, p = 0.005; NNH = 6 (3-50), p = 0.03); without adverse cognitive effects, which were measured in only one study.
Conclusions: Adjunctive topiramate seems to effectively improve total, positive, negative and general psychopathology symptoms in schizophrenia-spectrum disorders, reducing also weight and BMI compared to placebo or open antipsychotic treatment. Symptomatic efficacy was seen in patients treated with clozapine, a proxy for true resistance to standard antipsychotic treatment. Additional, larger studies are needed to confirm and extend these findings and to investigate why topiramate's weight reducing effects were attenuated in patients receiving clozapine compared to other antipsychotics.
Keywords: Schizophrenia, antipsychotics, topiramate, augmentation, postive and negative symptoms
Disclosure: C. Correll, **Part 1:** Actelion, Alexza, AstraZeneca, Biotis, Bristol-Myers Squibb, Cephalon, Desitin, Eli Lilly, Gerson Lehrman Group, GSK, IntraCellular Therapies, Lundbeck, Medavante, Medscape, Merck, Novartis, Ortho-McNeill/Janssen/J&J, Otsuka, Pfizer, ProPhase, Sunovion, Takeda, Teva, and Vanda, **Part 2:** AstraZeneca, Bristol-Myers Squibb, Cephalon, GSK, Merck, Otsuka, Pfizer, ProPhase, **Part 3:** AstraZeneca, Bristol-Myers Squibb, Otsuka, Pfizer, ProPhase, **Part 4:** BMS, Janssen/J&J, Otsuka; L. Maayan, **Part 4:** Eli Lilly and Pfizer; M. De Hert, **Part 1:** Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Pfizer and, Sanofi Aventis, **Part 4:** Janssen Cilag, Astra Zeneca, Eli Lilly; D. Cohen, Nothing to Disclose.

T150. Alcohol-induced Conditioned Place Preference in Healthy Moderate Drinkers

Emma L. Childs*, Harriet de Wit

The University of Chicago, Chicago, Illinois

Background: Alcohol drinkers form powerful associations with the places where drinking occurs. These learned associations, called contextual conditioning, influence all stages of alcohol abuse and addiction and represent a unique target for treatment, but they have not been studied in detail in humans. In this study, we examined *de novo* contextual conditioning between alcohol and the places where drinking occurs and its influence upon behavior and alcohol effects in the conditioned environment using a controlled human laboratory paradigm based upon well-established animal methodology.
Methods: Healthy men and women (N = 33) underwent six conditioning sessions, three with consumption of alcohol-containing drinks and three with drinks containing no alcohol (in randomised order). One group (paired group) always received alcohol (0.08g/kg) in one testing room and no-alcohol in another testing room, while another group (unpaired group) received alcohol and no-alcohol in each testing room. During the sessions, individuals completed subjective self-report questionnaires, and heart rate and blood pressure were monitored at 30 min intervals. Once all the sessions were complete, participants performed a drug-free behavioural preference test in which they were allowed to explore the two testing rooms moving freely between them while video recorders captured their motion. They then consumed a standard dose of alcohol (0.02g/kg) in one of the two testing rooms and rated their subjective state.
Results: In comparison to the unpaired condition, consuming alcohol in a consistent environment increased alcohol-induced feelings of amphetamine-like stimulation ($p < 0.05$) and feeling high ($p < 0.05$). In comparison to the unpaired group, participants in the paired group spent significantly more time in the alcohol-paired testing room at the drug-free test of preference ($p < 0.05$). In addition, paired group participants who consumed alcohol in the alcohol-paired room at test reported more positive and less negative subjective effects of alcohol than paired group participants who consumed alcohol in the no alcohol-paired room.
Conclusions: These findings indicate that humans, like animals, will spend more time in an environment previously paired with alcohol administration. Alcohol contextual conditioning enhances positive subjective responses and attenuates negative responses to the drug which may influence drug consumption in the conditioned environment. Together these preliminary findings with alcohol suggest a new approach to investigating the powerful effects of drug conditioning upon behaviour. This research is supported by a grant from ABMRF/ The Foundation for Alcohol Research and NIAAA AA020964.
Keywords: alcohol, context, conditioning, behaviour, human, subjective
Disclosure: E. Childs, Nothing to Disclose; H. de Wit, **Part 4:** Received a grant from Unilever for a research project unrelated to this abstract.

T151. Increased Developmental Serotonin Influences Response to Psychotomimetics in Adulthood

Caitlin E. McOmish*, Elena Y. Demireva, Natalie A. Diacovo, Alice M. Rolland, Jay A. Gingrich

Columbia University, New York, New York

Background: Serotonergic tone plays an important role in modulating neural pathway formation during development. This is illustrated by the paradoxical effects produced by postnatal administration of fluoxetine (a member of the selective serotonin reuptake inhibitor class of antidepressants). When administered during sensitive periods of development, rather than reducing affective phenotypes, fluoxetine has been shown to increase depression and anxiety-like behaviors in mice. These phenotypes are presumably a consequence of disrupting normal brain development, however elucidation of the precise nature of the neural anomalies and the full extent of the disruptive impact is ongoing. The serotonin 2A receptor ($5HT_{2A}$) is of interest as one of the post-synaptic targets that may be disrupted by postnatal fluoxetine treatment (PNFLX), as reducing $5HT_{2A}$ activity has anxiolytic effects. Here we tested the hypothesis that increased serotonergic tone during development leads to changes in adult $5HT_{2A}$ function.
Methods: Wildtype (WT) and $5HT_{2A}$ KO mouse pups were injected i.p with 10 mg/kg fluoxetine daily, from postnatal days 2 to 11. Behavioral analyses were performed on mice after they reached 3 months of age. Head twitch response (HTR) to hallucinogens was used as a proxy for $5HT_{2A}$ function. Mice were injected i.p with DOI (2 mg/kg) and placed in empty holding cages. The 25 minutes following the injection were scored manually for head-twitch (side-side, full body, and front back), ear scratches and tail rattling. Locomotor response to psychotomimetics and antipsychotics was performed in Kinder-Scientific Open Field Arenas. After a 30 minute baseline recording, animals were treated with vehicle, or an antipsychotic (Clozapine 1.5 mg/kg or M100907 2 mg/kg). All mice were given amphetamine 45 minutes after trial onset,

and locomotor response to this psychotomimetic was recorded. Prepulse Inhibition (PPI) was performed in Kinder Scientific Acoustic Startle Boxes. Acoustic startle to a 115 dB was determined by 40 startle only trials across the session. For the inhibition trials, prepulses of 4,8,12 and 16 dB above a background 70 dB white noise levels preceded a startle inducing tone of 115 dB (10 of each).
Results: Postnatal fluoxetine treatment (PNFLX) decreased the HTR in WT mice, suggesting decreased $5HT_{2A}$ function as a result of this developmental disruption. As has been previously shown, $5HT_{2A}$ KO mice showed no HTR response to DOI; PNFLX did not alter this. PNFLX treated mice display reduced amphetamine induced hyperlocomotor response in both WT and $5HT_{2A}$ KO mice. However, PNFLX treatment did not differentially affect response to antipsychotics. In WT mice, the response to amphetamine was attenuated by clozapine or M100907 (a $5HT_{2A}$ antagonist) administration. In $5HT_{2A}$ KO mice, M100907 had no effect. In these mice, clozapine exacerbated the amphetamine stimulated hyperlocomotion, possibly due to $5HT_{2C}$ antagonism. 5HT2A KO mice showed significantly reduced acoustic startle response (ASR) relative to WT mice. PNFLX did not affect this response. Baseline PPI was not affected by either PNFLX or 5HT2A genotype. Moreover, disruption of PPI response by MK-801 was found to be reduced, equally in all groups.
Conclusions: Serotonin signaling and the $5HT_{2A}$ receptor have independently been implicated in psychiatric conditions including depression, anxiety, OCD and schizophrenia. Affective behaviors in PNFLX mice have been extensively tested. Our analyses extend this, addressing the role of developmental serotonin in the etiology of other psychiatric conditions. Interestingly, while both $5HT_{2A}$ and PNFLX appear to play a role in the behavioral responses assessed, only in the HTR was there evidence for PNFLX modulation of $5HT_{2A}$ dependent behaviors. This could be due to changes in post-synaptic target neurons either at the level of the receptor and its downstream signaling or at a circuit level. Moreover, while it has been shown that $5HT_{2A}$ is imperative to the HTR, it has also been shown that this response can be modulated by other systems, including dopaminergic mechanisms. This is of relevance as the findings presented herein are consistent with altered response to dopaminergic stimulation: PNFLX treated mice show hyporesponsiveness to amphetamine treatment in the open field while MK801, a non-dopaminergic psychotomimetic, disrupted PPI equally in WT, $5HT_{2A}$ KO and PNFLX treated mice. These findings demonstrate a serotonin-dopamine interaction during development and raise new questions about how these two systems control the development and breadth of abnormal behavioral endophenotypes relevant to psychiatry.
Keywords: 5HT2A fluoxetine serotonin amphetamine hallucinogen
Disclosure: C. McOmish, Nothing to Disclose; E. Demireva, Nothing to Disclose; N. Diacovo, Nothing to Disclose; A. Rolland, Nothing to Disclose; J. Gingrich, Nothing to Disclose.

T152. Epigenetics, Neurodevelopment, and Risk for Anxiety and Depression in Model Rats

Sarah M. Clinton*, Rebecca K. Simmons, Matthew E. Glover, Phyllis C. Pugh, Huda Akil

University of Alabama-Birmingham, Birmingham, Alabama

Background: Individual differences in human temperament powerfully shape ability to cope with stress as well as vulnerability to mental illness. Our ongoing work utilizes rats to model individual differences in temperament to understand molecular and neuroanatomical changes in the developing brain that may put an individual at risk for a depressive/anxiety-like phenotype. The hippocampus emerged as a particularly important node in shaping temperament differences, as we found altered hippocampal volume, cell proliferation, gene expression, and epigenetic (DNA methylation) changes in the developing brain of "depression prone" versus "depression resistant" rats. The current experiments highlight similar changes in the developing amygdala – an area well-known for regulating emotion, in part via interconnections with the hippocampus.
Methods: In rats selectively-bred for differences in locomotor response to novelty, low novelty responders(bLR) exhibit high levels of behavioral inhibition, anxiety- and depression-like behavior, compared to high novelty responders (bHR), which are highly aggressive, impulsive and prone to drug-taking. The bLR/bHR phenotypes are highly predictable across generations and emerge as early as the second week of life. Brains were collected from developing bLR/bHR pups at three time points (postnatal days (P)7, 14, and 21). The amygdala was dissected, and RNA and DNA were extracted for Affymetrix microarray gene expression and Epigentek global DNA methylation assays, respectively.
Results: The microarray experiment revealed dramatic global gene expression differences in the developing amygdala of bLR vs. bHR rats. At P7 and P14, approximately 400 genes were differentially expressed between the strains, and by P21, nearly 700 genes were differentially expressed. At P7, 15% of altered genes were downregulated in bLR vs. bHR, while 85% was upregulated. This pattern dramatically changed at the later timepoints, with approximately 80% of altered genes being downregulated in bLR vs. bHR at P14 and P21, while approximately 20% were upregulated. The global DNA methylation assay revealed robustly increased DNA methylation in the amygdala of bLR (vs. bHR) rats specifically at P7. There were no group differences at the other ages (P14 and P21), and we did not see differences at any timepoint for several other brain areas, including the hippocampus, caudate putamen, or septum. Ongoing studies are evaluating methylation status of specific genes in P7 amygdala samples from bLR/bHR rats.
Conclusions: Our earlier work pointed to marked differences in developing hippocampus of bLR vs. bHR rats, suggesting a possible neurodevelopmental underpinning of their distinct behavioral phenotypes. Here we report remarkable bLR/bHR differences in the developing amygdala. Microarray results revealed substantial gene expression changes at P7 and P14 that expand with age (nearly doubling the number of genes changed at P21 vs. P14). This finding is quite interesting as the pattern differs from our prior microarray study in hippocampus; there we found robust bLR/bHR differences at P7 and P14, with extremely few changes at P21. We also discovered robustly increased global methylation in the P7 amygdala of bLR vs. bHR rats. DNA methylation is typically thought to suppress gene expression, so this dramatic DNA methylation difference may contribute to P14 and P21 gene expression differences where 80% of differing genes were downregulated in bLR vs. bHR rats. Ongoing work aims to identify specific gene targets that are differentially methylated in bLR/bHR rats, and determine whether manipulating methylation in the developing brain can ameliorate some aspects of the bLR/bHR phenotypes. Furthermore, we are also exploring possible differences in hippocampal-amygdala connectivity in developing bLR/bHR rats to identify neural circuit differences that correspond with observed molecular changes. Overall this body of work aims to provide insight into the possible genesis of individual differences in emotionality and related risks for the emergence of emotional disorders (e.g. the anxiety-prone nature of bLRs or drug addiction proclivity of bHRs), and delineate the role of epigenetic processes in these phenomena.
Keywords: methylation, amygdala, neurodevelopment, anxiety
Disclosure: S. Clinton, Nothing to Disclose; R. Simmons, Nothing to Disclose; M. Glover, Nothing to Disclose; P. Pugh, Nothing to Disclose; H. Akil, Nothing to Disclose.

T153. Phospholipase C Signaling within the Central Nucleus of the Amygdala Maintains Binge Alcohol Drinking by Mice

Justin A. Courson, Emily Lum, Karen K. Szumlinski*

University of California at Santa Barbara, Santa Barbara, California

Background: Earlier neuropharmacological data from our group demonstrated a necessary role for the activation of the mGluR1 and

mGluR5 subtypes of Group 1 metabotropic glutamate receptors (mGluRs) within the central nucleus of the amygdala (CeA) in maintaining excessive alcohol intake in a murine model of binge alcohol drinking. Binge alcohol intake by C57BL/6J mice elevates the expression of Group 1 mGluRs, Homer2, and the activational state of PKCε within the CeA. Intra-CeA infusions of selective mGluR1 and mGluR5 antagonists reduce binge alcohol drinking by mice and the "anti-binge" effects of mGluR1 and mGluR5 antagonists require intact Homer2a/b expression as they are not apparent in Homer2 null mutant mice. Moreover, the "anti-binge" effects of mGluR1/5 antagonists involve the translocation of PKCε, as they are not additive with those of a peptide inhibitor of this kinase. Group 1 mGluRs can activate a number of down-stream pathways through the stimulation of αq, αo and βγ signaling. However, immunoblotting and neuropharmacological studies failed to indicate a major role for βγ-mediated stimulation of PI3K within the CeA in regulating binge alcohol drinking. Thus, the present study sought to examine the role for αq-mediated stimulation of phospholipse C (PLC) in this regard and employed neuropharmacological approaches to examine the role for mGluR-PLC-PKCε signaling within the CeA in excessive alcohol intake.
Methods: We first examined for binge alcohol-induced changes in PLC expression using conventional immunoblotting approaches. For this, the total protein expression of PLC was determined in CeA and basolateral amygdala (BLA) tissue from C57BL/6J mice, sacrificed 24 hrs following a 30-day history of binge alcohol drinking under Drinking-in-the-Dark (DID) procedures (2 hrs access to 20% alcohol, at 3 hrs into the circadian dark cycle). Follow-up behavioral studies then examined the functional relevance of PLC activity for binge drinking. For these studies, groups of C57BL/6J mice were surgically implanted with bilateral guide cannulae aimed above the CeA. Upon the establishment of stable alcohol intake under DID procedures, mice were infused with the PLC antagonist U73122 alone (0-500 nM) or in combination with effective doses of the mGluR5 antagonist MTEP (50.7 mM), the mGluR1 antagonist JNJ16259685 (185 nM) or a Tat-ev1-2 PKCε inhibitor peptide (0.25 μl/side).
Results: Relative to water-consuming mice, a month-long history of binge alcohol intake elevated PLC levels within the CeA by approximately 30% [$t(22) = 2.75$, $p = 0.01$]. No such changes were detected within the BLA (*t*-test, n.s.). Pharmacological inhibition of CeA PLC activity by U73122 potently reduced binge alcohol drinking, with doses as low as 0.005 nM exerting significant effects [$F(6,86) = 4.74$, $p < 0.0001$]. Co-infusion of the 0.005 nM dose of U73122 and the mGluR5 antagonist MTEP or pretreatment with the the Tat-ev1-2 PKC inhibitor prior to U73122 infusion produced a reduction in alcohol drinking that was comparable to 0.005 nM U73122 alone. In contrast, co-infusion of the 0.005 nM dose of U73122 and the mGluR1 antagonist JNJ16259685 produced a greater reduction in drinking than that produced by U73122 alone.
Conclusions: To the best of our knowledge, these data are the first to indicate a necessary role for mGluR5-mediated activation of PLC-PKCε signaling within the CeA in maintaining excessive alcohol drinking in mice and pose alcohol-induced hyperactivity of mGluR5-mediating signaling through αq as a pathological state driving an animal to drink. While mGluR1 signaling within the CeA is clearly involved in regulating binge alcohol intake, the combination of previous data for PI3K inhibition and the present data for PLC inhibition do not support mGluR1-mediated stimulation of either αq/PLC or βγ/PI3K in this regard. Thus, future studies will examine the role for mGluR1-mediated stimulation of αo signaling within the CeA in the manifestation of excessive alcohol drinking.
Keywords: binge alcohol, phospholipase C, mGluR5, central nucleus of the amydala, mGluR1
Disclosure: J. Courson, Nothing to Disclose; E. Lum, Nothing to Disclose; K. Szumlinski, Nothing to Disclose.

T154. Juvenile Methylphenidate Interacts with Dopamine and Estrogen Levels to Modulate Dopamine Receptors in Prefrontal Cortex of Female Rats

Jodi Lukkes, Britta S. Thompson, Kai Sonntag, Susan L. Andersen*

McLean Hospital/Harvard Medical School, Belmont, Massachusetts

Background: Attention deficit hyperactivity disorder (ADHD) is partially characterized by reduced cortical levels of dopamine. Despite this observation, few studies have determined whether prefrontal dopamine levels differentially influence psychostimulant action by effecting dopamine receptor expression. Moreover, sex differences in ADHD symptoms tend to equalize during adolescence. As hormone levels begin to flux, reward dysfunction in girls with ADHD seems to parallel the rise and fall of estrogen. Low estrogen levels exacerbate drug craving associated with low dopamine. Elevated estrogen levels facilitate dopamine release, and thus may provide some symptom relief akin to that of the psychostimulants. Together, these observations suggest that estrogen may modify dopamine receptor function. In this study, we determined what role, if any, reduced dopamine levels during development have on dopamine and noradrenergic receptor mRNA development. In addition, we investigated whether estrogen stage modifies receptor mRNA levels in the late adolescent prefrontal cortex.
Methods: Sprague-Dawley rat pups ($n = 4$-6/group) were anesthetized by hypothermia and received a stereotaxic injection of either an aCSF vehicle or 6-OHDA (preceded by desipramine to protect noradrenergic terminals) into the prelimbic prefrontal cortex at postnatal day (P)9. Subjects were orally administered saline vehicle or methylphenidate (2 mg/kg) by ingestion between P20-35. Female rats were sacrificed at P60 in either a high (proestrous or estrous) or low estrogen (diestrous 1 or 2) state. The prelimbic prefrontal cortex was dissected, processed, and quantitative PCR was used to assess dopamine D1-5 and noradrenergic receptors 1a and 2a mRNA levels.
Results: A 2(depletion) x 2(treatment) x 2(estrogen) ANOVA revealed a number of significant findings. The three-way interaction was not significant for any of the receptors examined. However, main effects and a number of two-way interactions were observed. Low dopamine during development reduces mRNA for all receptors (p's < 0.05), but this effect strongly interacts with estrogen, which decreased receptor mRNA in sham controls but increases receptors in depleted subjects (p's < 0.01 for all receptors) with minimal effect of methylphenidate. Methylphenidate exposure did interact with estrogen levels to reduce D2 and alpha2a receptor mRNA ($F_{1,30} = 4.1$ and 3.9 respectively, $p < 0.05$), which decreased under low estrogen and was slightly elevated under high estrogen conditions relative to vehicle subjects.
Conclusions: Our data suggest that lower levels of dopamine during development reduce the expression of D1-5 dopamine receptors and noradrenergic receptors in the prefrontal cortex in late adolescence. Methylphenidate has a minimal effect on expression in these subjects but interacts strongly with estrogen to increase receptor expression. These data may explain worsened mood and drug craving during the luteal phase, when estrogen levels are lower. Juvenile treatment with methylphenidate may help reduce craving during this phase, but enduring effects will be strongest during higher estrogen phases (e.g., proestrous). Data from the sham controls are also consistent with this observation: methylphenidate lowers dopamine receptor density and we have shown increased preferences for cocaine-associated environments. Additional research is needed to understand the neurobiology of the interface between hormonal cycling and early drug exposure in females.
Keywords: ADHD, adolescent, methylphenidate, animal models, female
Disclosure: J. Lukkes, Nothing to Disclose; B. Thompson, Nothing to Disclose; K. Sonntag, Nothing to Disclose; S. Andersen, Nothing to Disclose.

T155. Ovarian Hormones Modulate Working Memory Related Hippocampal-DPLFC Connectivity in Women - A Positron Emission Tomography (PET) Study

Katherine Damme*, Shau-Ming Wei, Erica Baller, Jeffrey Bloch, Phillip Kohn, Shane Kippenhan, David Rubinow, Pedro Martinez, Peter Schmidt, Karen Berman

National Institute of Mental Health, Bethesda, Maryland

Background: There is considerable evidence suggesting that the gonadal steroid hormones, estradiol and progesterone, influence prefrontal (PFC) and hippocampal dependent cognitive functions such as working memory, but the underlying neurophysiological mechanisms are unclear. Preclinical studies demonstrate that estrogen receptors are highly expressed in the hippocampus and PFC regions, and that estradiol increases adult neurogenesis, provides neuroprotection, and facilitates memory formation. In addition, estradiol is an important mediator of axonal guidance, dendritic aborization and synaptogenesis, which in turn, modulate functional connectivity, the collaborative actions of neural systems, between estradiol rich areas and other brain regions. There is also evidence indicating that the effects of progesterone in the aforementioned regions are similar to that of estradiol, but results have been inconclusive. Working memory is characterized by distinct fronto-temporal functional connectivity, and disturbed hippocampal-dorsolateral PFC interactions have been reported in many psychiatric disorders that show sexually dimorphic expressions. In order to identify the individual effects of estradiol and progesterone on working memory-dependent functional connectivity, we used PET together with a cognitive task that accesses both PFC and hippocampal circuitries to study healthy volunteers during a six-month pharmacologically-controlled hormone manipulation protocol based on the gonadotropin-releasing hormone agonist Lupron. This protocol allowed us to carefully control the hormonal milieu to which each woman's brain was exposed.
Methods: Forty-four healthy, regularly menstruating women with no psychiatric history underwent three neuroimaging sessions consisting of 14 n-back rCBF scans (10 mCi $H_2^{15}O$ /scan, seven scans each during 2-back and 0-back). Scan sessions occurred during: (1) Lupron alone, (2) Lupron plus estradiol addback, and (3) Lupron plus progesterone addback. After preprocessing, first-level activation maps (2bk - 0bk) for each participant were created. Next, in order to examine working memory-related frontotemporal functional connectivity, rCBF was extracted from a bilateral hippocampal seed region and used as a regressor in voxel-wise correlational analyses within an independently derived bilateral dorsolateral prefrontal cortex (DLPFC) mask (as cytoarchitechtonically defined in standard stereotaxic space in post-mortem human brain). These correlation maps between rCBF activation values in the bilateral hippocampal seed region and those in DLPFC were then compared across hormone conditions. Results were viewed at an exploratory threshold of $p < 0.005$, uncorrected.
Results: There were no significant differences in working memory performance across hormone conditions. In addition, measurements of serum estradiol and progesterone confirmed hormonal suppression during the Lupron alone condition, as well as replacement to physiological levels of the appropriate gonadal steroid during each add-back condition. There was a main effect of hormone condition on functional connectivity of the hippocampal with both left and right DLPFC: the expected working memory-related negative correlation was observed during estradiol add-back ($r = -0.34$, $p = 0.02$), and during progesterone add-back there was a positive hippocampal-right DLPFC correlation ($r = 0.38$, $p = 0.009$), but there was no significant correlation during ovarian suppression with Lupron alone ($r < 0.25$, $p > 0.05$).
Conclusions: Our data demonstrate that ovarian steroids modulate hippocampal-PFC functional connectivity, consistent with a role for these hormones in modulating hippocampus at the cellular level. Interestingly, our findings indicate that progesterone and estradiol have opposite effects on this *in vivo* measure of hippocampal-DLPFC cooperatively, substantiating the complex influence of gonadal steroids in brain circuitry and calling for further clinical and preclinical investigation.
Keywords: Estrogen, Progesterone, PET, imaging, Hippocampus, DLPFC, Working Memory
Disclosure: K. Damme, Nothing to Disclose; S. Wei, Nothing to Disclose; E. Baller, Nothing to Disclose; J. Bloch, Nothing to Disclose; P. Kohn, Nothing to Disclose; S. Kippenhan, Nothing to Disclose; D. Rubinow, Nothing to Disclose; P. Martinez, Nothing to Disclose; P. Schmidt, Nothing to Disclose; K. Berman, Nothing to Disclose.

T156. Effects of Cocaine Self-administration and Extinction on Astrocyte Content and Protein Expression in the Nucleus Accumbens, and Relationship to Reinstatement

Kathryn Reissner*, Heather Boger, Peter Kalivas

Medical University of South Carolina, Charleston, South Carolina

Background: Recent studies show that the astroglial high affinity glutamate transporter is downregulated following self-administration of cocaine, heroin, and nicotine. Moreover, restoration of GLT-1 with the antioxidant N-acetylcysteine (NAC) or the beta-lactam antibiotic ceftriaxone decreases cocaine reinstatement in the self-administration model of drug abuse, and restores measures of glutamate homeostasis. In fact, restoration of GLT-1 is necessary in order to observe the therapeutic effect of NAC. We have also found that the glial modulator propentofylline (PPF) decreases cocaine reinstatement in the self-administration model of drug abuse (unpublished observations). These findings collectively suggest effects of drug self-administration on astrocytes which may contribute to the behavioral and neural pathologies associated with addiction. Thus, we report here three experiments designed to more thoroughly establish how cocaine self-administration affects expression of astroglial proteins and how modulation of these proteins may influence reinstatement behavior.
Methods: Male Sprague-Dawley rats were trained to self-administer cocaine on an FR1 schedule during 2 h sessions each day, for approximately two weeks. A lever press resulted in a cocaine infusion (0.2 mg per infusion, or yoked saline), as well as presentation of light and tone drug-paired cues. Following self-administration, rats entered an extinction training phase, during which a lever press no longer resulted in drug or drug-paired cues. For Experiment 1, during the last 6 days of extinction rats received an injection of propentofylline (10 mg/kg, i.p.) or saline 30 min prior to the extinction session. Then, tissue samples were taken from the nucleus accumbens (NAc) and prefrontal cortex for Western blot analysis. For Experiment 2, animals were trained to self-administer cocaine or yoked saline, and following deep sedation with pentobarbital were prepared for quantitative immunohistochemistry of GFAP in serial sections from the NAc. Lastly, for experiment 3, cocaine self-administering animals received a microinjection of AAV1 expressing either GLT-1 or GFP control prior to initiation of three weeks of extinction training and cue-primed reinstatement.
Results: Experiment 1: we found that in addition to GLT-1, the astroglial protein glial fibrillary acidic protein (GFAP) is also down regulated in the NAc core and shell, but not the prefrontal cortex, following cocaine self-administration and extinction, relative to saline controls. Moreover, GLT-1 expression is partly restored in the NAc core and fully restored in the shell by PPF; the cocaine-mediated reduction in GFAP is also partly restored by PPF. Experiment 2: we hypothesize that quantitative immunohistochemistry will reveal decreased GFAP content as observed by Western blot. These results in progress will determine more clearly whether this decrease is exclusively densitometric or reveals a decrease in astrocyte number in the core and shell as well. Experiment 3: Infusion of AAV1 expressing GLT-1 results in a decrease in cue-primed reinstatement, while expression of GLT-1 in the shell is without effect.
Conclusions: Results presented here indicate that beyond GLT-1, cocaine self-administration and extinction also result in decreased expression of GFAP in the NAc, suggestive of a generalized decrease in astroglial content and/or activation. This hypothesis is

being tested with quantitative immunohistochemistry for GFAP following cocaine versus saline administration. This is in contrast with studies which have indicated an increase in GFAP expression, reflective of reactive gliosis, following noncontingent administration. Furthermore, preliminary results indicate that viral overexpression of GLT-1 in the core, but not the shell, impairs cue-primed reinstatement. These studies indicate that targeting cocaine-induced deficits in astroglial function may reverse drug dependent cellular abnormalities and provide a means of therapeutic intervention for drug seeking.
Keywords: cocaine, addiction, astrocyte, glutamate, GFAP
Disclosure: K. Reissner, Nothing to Disclose; H. Boger, Nothing to Disclose; P. Kalivas, Nothing to Disclose.

T157. Effects of Early Prefrontal Cortex NMDA Receptor Dysfunction on Impulsivity in Adulthood

Janet Finlay*, Ginger Dunham, Robert Greene

Western Washington University, Bellingham, Washington

Background: Glutamate N-methyl-D-aspartate (NMDA) receptors in the prefrontal cortex (PFC) play a role in normal cognitive function. In adult rodents, acute and chronic administration of NMDA receptor antagonists impairs cognitive function. Little is known about the functional impact of PFC NMDA receptor dysfunction sustained early in development. We are examining the effects of chronic NMDA receptor dysfunction induced in adolescence or adulthood on adult cognitive function using a 5-choice serial reaction time task (5CSRTT).
Methods: Localized deletions of a requisite exon of the NMDA receptor NR1 subunit were induced on postnatal day 29 (PN29; adolescence; n = 6/group) or PN70 (adulthood; n = 4/group) by infusion of AAV-Cre into the PFC of floxed NR1 transgenic mice. In adulthood, all mice were trained on a 5CSRTT that required them to exhibit a nosepoke in response to a brief, random illumination of one of five nosepoke apertures.
Results: Under baseline conditions [0.8 s stimulus duration and 5.0 s intertrial interval (ITI)], control and deleted mice achieved comparable accuracy (PN29: 87 ± 2% and 82 ± 3%, respectively and PN70: 85 ± 2% and 80 ± 2%, respectively). Premature responding was assessed as a measure of impulsivity. Under baseline conditions, PN29 deleted mice exhibited increased premature responding relative to age-matched controls (3.2 ± 0.4 versus 1.2 ± 0.3, respectively). In contrast, PN70 deleted mice exhibited premature responding under baseline conditions that was similar to age-matched controls (1.9 ± 0.3 versus 2.1 ± 0.2, respectively). Following acquisition of stable baseline responding, mice were tested under conditions of varying ITIs, stimulus duration, stimulus intensity, and white noise. The most robust differences between deleted and control mice occurred during challenge with longer ITIs (randomly presented 5, 6, 7 and 8 s ITIs). Under the longer ITI conditions, PN29 deleted mice exhibited a greater increase in premature responding than age-matched controls (19.2 ± 3.0 versus 8.0 ± 2.5, respectively). In contrast, the latter effect was not observed in mice sustaining deletions on PN70.
Conclusions: The present study indicates that chronic dysfunction of NMDA receptors sustained in adolescence, but not adulthood, results in impulsivity in adulthood that was characterized by the emergence of inappropriate responding. These findings are consistent with the hypothesis that PFC NMDA receptors play a role in cognitive inhibition and that NMDA receptor dysfunction early in development may result in impulsivity associated with adult psychiatric illness.
Keywords: glutamate schizophrenia mouse attention ADHD
Disclosure: J. Finlay, Nothing to Disclose; G. Dunham, Nothing to Disclose; R. Greene, Nothing to Disclose.

T158. Guided by Your Heart: Cardiac Cycle Modulates the Awareness and Perceived Intensity of Fear Stimuli

Sarah N. Garfinkel*, Hugo D. Critchley

Brighton and Sussex Medical School, Sussex, United Kingdom

Background: Cognitive and affective processing can be influenced by bodily states of arousal. Cardiovascular arousal is signalled by bursts of afferent neural activity from arterial baroreceptors at systole (cardiac ejection period) that encode the strength and timing of individual heartbeats. We tested if this specific channel of interoceptive information alters awareness and reported intensity of fear stimuli while also examining the underlying neural circuitry.
Methods: In 20 healthy participants, stimulus presentation was time-locked to specific points in the cardiac cycle to investigate how processing at systole vs. diastole modified perceptual awareness and emotional judgements. Using a modified Attentional Blink paradigm (to induce stimulus masking), we tested if timing stimuli to systole (relative to diastole) modulated awareness via 'breakthrough perception' of faces. In an emotional judgement study, we tested whether faces presented at systole (for 100 ms, relative to presentation at diastole) modulated subsequent VAS intensity ratings of fearful and neutral faces. We recorded brain activity via fMRI at 1.5T.
Results: In the first study, we observed enhanced attentional breakthrough of fearful vs. neutral face stimuli [$t(19) = 3.3$, p-.004], but only for trials time locked to systole [emotion x cardiac cycle interaction [$F(1,19) = 7.466$, $p = .013$]. Emotional enhancement of fear face detection (relative to neutral) was blocked for trials beginning at diastole [$t(19) = .49$, $p = .63$]. In the second study, reported intensity of fearful faces increased at systole. Preliminary fMRI analyses suggest amygdala and PAG mediate this effect (emotion x cardiac timing interaction; amygdala [-12 -2 -14] $Z = 3.90$; 174 voxels; PAG [-8-26 -10] $Z = 2.8$, 59 voxels).
Conclusions: Short-term interoceptive bodily fluctuations gate the attention-dependent detection and emotional impact of salient stimuli. Our observations highlight an important channel through which visceral state impacts cognitive and affective processing.
Keywords: Cardiac cycle, aroreceptor, attention, emotion
Disclosure: S. Garfinkel, Nothing to Disclose; H. Critchley, Nothing to Disclose.

T159. Insight, Treatment Outcomes and Recovery in First-episode Schizophrenia

Ofer Agid*, Cynthia Siu, Robert B. Zipursky, Gary Remington

University of Toronto, Toronto, Ontario, Canada

Background: Lack of insight or awareness of illness is prevalent in schizophrenia and a barrier to effective treatment (Mohamed et al 2009). There are, however, controversies regarding the impact insight can have on clinical symptoms, neurocognitive impairment, functional outcome, and subjective quality-of-life (QOL). Previous studies have reported mixed or even contradictory results due to ambiguities in concepts, causality and interpretation (Lysaker et al 2007). The role of insight in predicting treatment outcomes is an important area of investigation, and the objective of this study was to investigate cross-sectional relationships between insight and cognitive performance, social functioning, and subjective QOL rating in patients with first-episode schizophrenia who had attained symptom remission.
Methods: A total of 65 patients from two first-episode patient cohorts were investigated. Inclusion criteria included: 18-35 years of age, DSM-IV diagnosis of schizophrenia confirmed by the Mini International Neuropsychiatric Interview, and treatment for $\leqslant 1$ year. Patients' clinical status was assessed using the PANSS (Cohort 1) or BPRS (Cohort 2). Insight was measured using the

Schedule for Assessment of Insight (SAI), while cognitive functioning was evaluated using BACS (in Cohort 1 only). Functional performance was evaluated by SOFAS and the Social Functioning Scale (SFS). Subjective patient-reported outcomes were assessed using the Satisfaction with Life Scale (SWLS) and World Health Organization Quality of Life scale (WHOQOL-BREF, Cohort 1 only). Regression analysis was applied to investigate the relationships among these factors. No multiplicity adjustment was made in this exploratory analysis.

Results: The study sample consisted of two patient cohorts with first-episode schizophrenia (N = 34 in Cohort 1, N = 31 in Cohort 2) with a mean age was 27.2 years. Patients in both cohorts demonstrated good levels of insight (SAI total score = 11.4, SD = 2.6), and did not experience depressed mood symptoms (mean CDS score = 1.0; SD = 1.4). Despite high levels of insight and symptom remission, the mean BACS composite z-score (Cohort 1 only), standardized to healthy controls, was -2.05 (SD = 1.27), indicating patients performed at 2 SD below the normative sample. The overall median SOFAS score was 50 (IQR 45 to 60, N = 61), indicating moderate to serious impairment in social and occupational functioning in a majority of patients. Patients in both cohorts also experienced marked functional impairment, as measured by the Social Functioning Scale domains, being significantly lower on social engagement (95.9, SD = 16.8 for Patients vs. 115.5, SD = 14.0 for Controls), interpersonal communication (107.3, SD = 27.7 vs. 141.4, SD = 8.1), recreation (89.6, SD = 16.4 vs. 112.6, SD = 14.7), pro-social (100.0, SD = 18.9 vs. 118.7, SD = 8.7), and employment (102.9, SD = 6.7 vs. 120.6, SD = 2.9) scores compared to normal controls ($p < 0.05$). In the 2 patient cohorts, there was a significant correlation between the overall SAI insight score and G12 of the PANSS ($p < 0.05$). Higher level of insight was associated with increased cognitive performance (BACS total score), verbal memory and processing speed (all $p < 0.05$). Level of insight into illness as well as verbal memory performance were inversely related to both Interpersonal Communication (an objective Social Functioning domain score, $p < 0.05$) and lower Social Relationship (a subjective WHOQOL-BREF domain score, $p < 0.05$). Interpersonal Communication and Social Relationship were positively correlated ($p < 0.05$). The inverse relationship between insight into illness and subjective QOL rating in Social Relationship can be explained, in part, by the significant Interpersonal Communication Social Functioning factor, but the proportion of variations explained was small (16.5%, $p < 0.05$ in path analysis). Relationships between other social functioning and subjective QOL domains were not significant. Neither insight nor cognitive performance were directly correlated with life satisfaction SWLS scores.

Conclusions: Our findings suggest that despite good insight, symptom remission and lack of depression, there is significant impairment in neurocognitive and social functioning in first-episode schizophrenia. Higher levels of insight were associated with better cognitive performance, while both insight and verbal memory were inversely related to an objective measure of interpersonal communication (a domain of the Social Functioning Scale) and subjective measure of social relationships (a domain of the WHOQOL-BREF). Further research is needed to confirm these results using larger sample size and to investigate the role of other intervening variables such as medication adherence and longitudinal changes/outcomes. References:* Mohamed S, Rosenheck R, McEvoy J, Swartz M, Stroup S, Lieberman J A. Cross-sectional and longitudinal relationships between insight and attitudes toward medication and clinical outcomes in chronic schizophrenia. Schizophr Bull 2009; 35: 336-346. Lysaker P, Paul H, Kelly D. Insight, outcome and recovery in schizophrenia spectrum disorders: an examination of their paradoxical relationship. Curr Psychiatry Rev 2007; 3: 65-71.

Keywords: schizophrenia insight quality-of-life first-episode cognition

Disclosure: O. Agid, Nothing to Disclose; C. Siu, Nothing to Disclose; R. Zipursky, Nothing to Disclose; G. Remington, Nothing to Disclose.

T160. Precision Delivery of Viral Vectors within Discrete Brain Substructures of the Rodent

Miles G. Cunningham*, Sivan Subburaju, Andrew Coleman, Nand Kishore, Francine Benes

McLean Hospital, Harvard Medical School, Belmont, Massachusetts

Background: As our methods in neurobiology become increasingly sophisticated, our ability to surgically target discrete brain regions accurately and reproducibly has become essential. Gene transfer technology is a case in point, as it holds promise for augmenting or suppressing the expression of specific proteins and reversing biochemical defects. This requires precise delivery of very small, precise volumes of vector solution within substructures or specific cell groups or cell layers within the brain of experimental animals. Traditional delivery methods are frequently imprecise and impose trauma to the microenvironment of the area of interest, resulting in either failure of the experiment or requiring large numbers of trials and/or animals to generate sufficient group sizes to establish statistical significance. Here we describe practical methods used in our laboratory to dependably target the hippocampal stratum oriens, measuring less than 200 microns in the medial-lateral coordinate, with microvolumes of lentiviral vector.

Methods: Precision stereotaxic surgery was performed on post-natal day 45 male Sprague Dawley rats using either a MyNeuroLab manual stereotaxic instrument or a Leica Angle Two instrument. Upon preparation of the surgical field exposing the skull surface, a unified reference point ("URP") was interpolated using four landmarks: the interaural line, bregma, lambda, and the midpoint between the temporal ridges. From this URP, a surrogate viral solution (0.1 micron latex microspheres) was injected at coordinates determined from a brain atlas using a pulled borosilicate pipette having a long, gently tapering shank and a final tip diameter of 30 microns. The micropipette was secured to the stereotaxic manipulator arm and was connected with tubing leading to a 10 microL syringe controlled by an infusion pump. Microspheres were injected at the volume and rate intended for the vector, thus allowing accurate assessment of placement and behavior of similar-sized particles at specific volumes and at specific infusion rates. After the test injection, the brain was perfused, snap-frozen, and sectioned in 100 micron serial cryostat sections, thus generating an "atlas" specific for our particular experimental animal. Sections were stained with neutral red and cover-slipped. Using a micrometer, the coordinates were revised, and the test injection was repeated. This process was repeated until three consecutive "hits" were achieved.

Results: Coordinates were refined using microsphere test injections, and the optimal volume for this site was found to be 400 nL with a delivery rate of 100 nL per minute. Trauma to the injection site was undetectable. Efficiency of transfection, as assessed with expression of green fluorescent protein, was dependable and robust. The manual stereotaxic instrument proved adequate, however, the digital instrument reduced surgery time by 50% and allowed greater accuracy and consistency. For these experiments, animals received bilateral injections, and electrophysiology was performed using a slice preparation. With optimization of apparatus and methods, virtually every animal provided tissue with well-targeted vector.

Conclusions: Gene transfer to distinct neural populations is rapidly becoming an important approach for the study, and ultimately the treatment, of an array of brain diseases. Delivery of these vectors, or any neuroactive agent, merits careful planning and protocol. The properties of the injectate, the method of delivery, as well as the anatomy of the target must be considered for any particular investigation. Experimental validity as well as efficiency in terms of time, cost, and animal use can be assured with scrupulous design and exacting method.

Keywords: stereotaxic, viral vector, gene therapy, microinjection

Disclosure: M. Cunningham, Nothing to Disclose; S. Subburaju, Nothing to Disclose; A. Coleman, Nothing to Disclose; N. Kishore, Nothing to Disclose; F. Benes, Nothing to Disclose.

T161. Genetic Variation in Endocannabinoid Signaling Moderates the Association between Childhood Maltreatment and Amygdala Habituation

Ryan Bogdan*, Caitlin E. Carey, Emily M. Drabant, Arpana Agrawal, Sean D. Kristjansson, Ahmad R. Hariri

Washington University, St. Louis, Missouri

Background: The fatty acid amide hydrolase (FAAH) enzyme provides rate-limiting degradation of the endocannabinoid anandamide, which is involved in modulating threat-related amygdala function and related behaviors such as fear extinction (Gunduz-Cinar et al., *Molecular Psychiatry* 2012). The 385A allele of a common human *FAAH* polymorphism (rs324420; C385A) results in relatively reduced FAAH expression and, presumably, enhanced anandamide signaling. Consistent with these effects, the A allele predicts reduced threat-related amygdala reactivity, increased amygdala habituation, and decreased self-reported stress reactivity (Gunduz-Cinar et al., *Molecular Psychiatry* 2012). Thus, this polymorphism is positioned to bias both neural and behavioral responsiveness to threat and stress. Here, we test this possible moderating role of FAAH rs324420 by examining its impact on the relationship between amygdala habituation to threat and the experience of early stress as indexed by self-reported childhood trauma and maltreatment.
Methods: Young adults ($n = 280$) enrolled in the ongoing Duke Neurogenetics Study completed an assessment of threat-related amygdala reactivity using BOLD fMRI and completed self-report measures including the Childhood Trauma Questionnaire. Single-subject BOLD parameter estimates were extracted from functional clusters in the basolateral amygdala showing a linear decrease over time (i.e., habituation) at an FWE corrected voxel threshold of $p < 0.05$ and cluster extent threshold of $\geqslant 10$ contiguous voxels. DNA was collected via saliva and genotyping of rs324420 was conducted by 23andMe using a custom array. Main effects of genotype and childhood maltreatment, as well as their interaction were examined on amygdala habituation. Self-reported ethnicity, gender, and the presence of psychopathology as assessed by clinical interview were entered as covariates.
Results: After accounting for possible confounding effects of our covariates and main effects of genotype and maltreatment, there was a significant interaction between *FAAH* genotype x maltreatment on amygdala habituation ($F(1,270) = 4.58$, $p = .03$). At relatively high levels of childhood maltreatment, 385A carriers had significantly reduced amygdala habituation relative to C385 homozygotes. Moreover, these effects remained significant in the right, but not left, amygdala when restricting analyses to individuals of European descent ($n = 140$).
Conclusions: Here we show that a genetically driven bias for enhanced anandamide signaling interacts with elevated levels of childhood maltreatment to predict reduced amygdala habituation in response to threat. Specifically, the 385A allele was associated with greater habituation at low levels of maltreatment but with lesser habituation at higher levels of maltreatment. In contrast, amygdala habituation in C385 homozygotes was unrelated to levels of maltreatment. This pattern is consistent with a "plasticity" model wherein effects of a functional genetic polymorphism vary with contextual and other moderating variables. With regards to FAAH rs324420, it appears that the 385A allele may not globally confer resilience to stress-related psychopathology but rather bias responsiveness to challenge for better, or worse. Mechanistically, the differential impact of FAAH rs324420 on amygdala habituation may reflect the biasing of specific endocannabinoid pathways by stress. Recent non-human animal research (Hill et al., *PNAS* 2010) has shown that repeated stress reduces anandamide levels across corticolimbic regions, while the endocannabinoid arachidonoylglycerol (2-AG) is selectively increased within the basolateral amygdala. Interestingly, fear extinction training in animals increases anandamide, but not 2-AG, levels in the basolateral amygdala. Accordingly, childhood maltreatment may be associated with reductions in anandamide and increases in 2-AG levels within the basolateral amygdala creating competition for endocannabinoid receptor binding and interfering with anandamide-related fear extinction. Given a disposition conferring enhanced anandamide relative to 2-AG signaling in *FAAH* 385A carriers, these individuals may be particularly susceptible to stress-related reductions in anandamide and increases in 2-AG signaling and hence, blunted amygdala habituation and potential vulnerability to stress-related psychopathology. An alternative, though not mutually exclusive mechanism, may be related to hypothalamic-pituitary-adrenal axis function. Specifically, inhibition of anandamide signaling is critical for preventing basal hypercortisolemia in rodents in response to repeated stressors (Hill et al., *PNAS* 2010). Thus, the elevated anandamide signaling conferred by the *FAAH* 385A allele may promote the development of basal cortisol hyperactivity, which is associated with childhood maltreatment, and linked to sustained amygdala response to threat.
Keywords: Endocannabinoid, Amygdala, Threat, Anxiety, FAAH
Disclosure: R. Bogdan, Nothing to Disclose; C. Carey, Nothing to Disclose; E. Drabant, **Part 1:** Emily Drabant is currently employed by 23 and Me, **Part 3:** Emily Drabant is currently employed by 23andMe; A. Agrawal, **Part 4:** AA receives peer-reviewed grant funding from ABMRF/Foundation for Alcohol Research which receives contributions from the alcoholic beverages industry; S. Kristjansson, **Part 4:** SDK receives peer-reviewed grant funding from ABMRF/Foundation for Alcohol Research which receives contributions from the alcoholic beverages industry; A. Hariri, **Part 1:** I received a consultant payment from Zinfandel Pharmaceuticals, Inc. in 2010, I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University, which is for research unrelated to the present work, **Part 4:** I receive supplemental salary support from Takeda Pharmaceutical Company Limited through an ongoing research agreement between the company and Duke University, which is for research unrelated to the present work.

T162. A Randomized, Double-blind, Placebo-controlled Add-on Treatment of Benzoate, a D-amino Acid Oxidase Inhibitor, for Schizophrenia

Guochuan Emil. Tsai*, Hsien-Yuan Lane, Michael F. Green

UCLA School of Medicine, Pasadena, California

Background: In addition to dopaminergic hypothesis, hypofunction of N-methyl-D-aspartate receptor (NMDAR) plays a critical role in the pathophysiology of schizophrenia. Enhancing NMDAR-mediated neurotransmission has been regarded as a novel treatment approach. To date, several trials on adjuvant NMDA-enhancing agents, including coagonists, glycine, D-serine, D-alanine, as well as glycine transporter I inhibitor, sarcosine and bitopertin, revealed beneficial but limited efficacy. D-serine is more potent than glycine as the neurotransmitter for the coagonist site of the NMDAR; and D-amino acid oxidase (DAAO), a flavoenzyme of peroxisomes existing in CNS, is responsible for degrading D-serine and D-alanine. There are more than 30 studies demonstrate the association of DAAO and DAAO modulator, G72, with schizophrenia. Another method to enhance NMDA function is to raise the levels of DAA by blocking their metabolizing enzyme, DAAO. The proof of principle study for DAAO inhibition therapy is a clinical trial in schizophrenia population. Sodium benzoate is a DAAO inhibitor. To establish that DAAO inhibition is a novel therapeutic approach for the treatment of schizophrenia and further substantiate the hypoNMDA hypothesis of schizophrenia, we examined the efficacy and safety of add-on treatment of sodium benzoate in chronically stable schizophrenia patients. Due to the critical role NMDA system plays in cognition and memory, we also hypothesize that neurocognition can be improved by enhancing NMDA function via DAAO inhibition.
Methods: We conducted a randomized, double-blind, placebo-controlled trial in fifty-two patients with chronic schizophrenia who have been stabilized with antipsychotics for 3 months or longer. They received six weeks of add-on treatment of 1 gram/d sodium benzoate or placebo. The outcome measures included Positive and Negative Syndrome Scale (PANSS), Scales for the Assessment of Negative

symptoms (SANS), Global Assessment of Function (GAF), quality of life (QOL), and 7 cognitive domains recommended by Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). Clinical efficacy and side-effects were assessed biweekly. Cognitive functions were measured before and after treatment. Mean changes in clinical assessment were assessed using the mixed-model repeated measure methods with treatment, visit and treatment-visit interaction as fixed effects. For assessing the general cognitive ability of the patients, an overall composite T score that included the 6 domains of neurocognition was calculated by standardizing the sum of T scores.

Results: Benzoate treatment produced greater improvement in PANSS total (effect size, $d = 1.76$) PANSS subscales (positive 1.83, negative 1.44, general 1.29, cognitive 1.05), SANS (1.25), GAF (1.35), QOL (1.66), CGI (1.20) and HDRS (0.84). After 6-week treatment, the benzoate treatment also significantly improve the overall neurocognition (0.53); specifically in speed of processing (0.63), visual learning and memory (0.55), as well as verbal learning and memory (0.41) but not other domains. Benzoate was well tolerated without significant side-effects.

Conclusions: Overall, benzoate treatment gives rise to a favorite profile of improvement in main clinical symptoms and neurocognition. It represents a novel therapeutic target to develop new pharmacotherapy for the treatment of symptoms and improvement of cognitive functioning in schizophrenia. In this study, we demonstrated that sodium benzoate, a DAAO inhibitor, can improve a wide variety of symptom domains of schizophrenia. The effect sizes we observed are larger than other trials of NMDA-enhancing agents, mostly <0.5. These large effect sizes can be due to the good CNS bioavailability of benzoate (vs. the other small polar amino acids tested before). Also, the benzoate treatment inhibits the breakdown of D-serine and facilitates the efficiency of this strong co-agonist at NMDA receptor, as D-serine has a similar anatomical distribution to NMDAR in the forebrain. NMDAR regulates synaptic plasticity, memory, and cognition. Thus, attenuation of NMDAR-mediated neurotransmission can result in loss of neuronal plasticity and cognitive deficits. Hypo-NMDA function induced by NMDA receptor antagonists is neurotoxic and may account for deterioration and brain atrophy in schizophrenia. Accordingly, NMDA-enhancing agents are supposed to work as not only antipsychotics but also cognitive enhancers in schizophrenia that can mitigate the neurotoxic effect of NMDA antagonism. Preservation and even enhancing cognitive functioning have recently been recognized as a critical therapeutic goal. Our findings in neurocognition point to a novel approach to reach this goal.

Keywords: D-serine, cognition, MATRICS

Disclosure: G. Tsai, Nothing to Disclose; H. Lane, Nothing to Disclose; M. Green, Nothing to Disclose.

T163. Drug Cue-induced Dopamine Release in Amygdala and Hippocampus: A High-resolution PET [18F]Fallypride Study in Cocaine Dependent Participants

Aryandokht Fotros*, Kevin Casey, Kevin Larcher, Jeroen Verhaeghe, Sylvia Cox, Paul Gravel, Andrew Reader, Alain Dagher, Chawki Benkelfat, Marco Leyton

McGill University, Montreal, Quebec, Canada

Background: Drug related cues are potent triggers for relapse in people with cocaine dependence. Dopamine release within a limbic network of striatum, amygdala and hippocampus has been implicated in animal studies, but in humans it has been possible to test the first region only. The objective here was to measure effects in the amygdala and hippocampus using high-resolution PET with [^{18}F]fallypride.

Methods: Twelve cocaine dependent volunteers (mean age: 39.6 ± 8.0; years of cocaine use: 15.9 ± 7.4) underwent two PET [^{18}F]fallypride scans with a Siemens HRRT camera, one with exposure to neutral cues and one with cocaine cues. [^{18}F]Fallypride non-displaceable binding potential (BP_{ND}) values were derived for five regions of interest (ROI) (ventral limbic striatum, associative striatum, sensorimotor striatum, amygdala, and hippocampus). Subjective responses to the cues were measured with visual analog scales and grouped using principal component analysis.

Results: Individual differences in the cue-induced craving factor predicted [^{18}F]fallypride responses in the ventral limbic ($r = 0.581$, $p = 0.048$), associative ($r = 0.589$, $p = 0.044$) and sensorimotor striatum ($r = 0.675$, $p = 0.016$); the greater the craving, the greater the [^{18}F]fallypride response. When participants were split into craving responders ($n = 6$) and non-responders ($n = 6$), drug cue exposure significantly decreased BP_{ND} values in the craving group in all five ROI (limbic striatum: $p = 0.019$, associative striatum: $p = 0.008$, sensorimotor striatum: $p = 0.004$, amygdala: $p = 0.040$, and right hippocampus: $p = 0.025$), but not in the non-responders.

Conclusions: To our knowledge this study provides the first evidence of drug cue-induced dopamine release in the amygdala and hippocampus in humans. The preferential induction of dopamine release among cue-responders suggests that these aspects of the limbic reward network might contribute to drug seeking behavior.

Keywords: addiction, craving, reward, striatum, limbic, conditioning

Disclosure: A. Fotros, Nothing to Disclose; K. Casey, Nothing to Disclose; K. Larcher, Nothing to Disclose; J. Verhaeghe, Nothing to Disclose; S. Cox, Nothing to Disclose; P. Gravel, Nothing to Disclose; A. Reader, Nothing to Disclose; A. Dagher, Nothing to Disclose; C. Benkelfat, Nothing to Disclose; M. Leyton, Nothing to Disclose.

T163. Unlike Serotonin, Clozapine Induced, 5-HT2AR-mediated Signaling and Behavioral Events are Beta-arrestin2 Independent

Cullen L. Schmid*, John M. Streicher, Laura M. Bohn

The Scripps Research Institute, Jupiter, Florida

Background: The atypical antipsychotic clozapine mediates some of its biological effects through interactions with the serotonin 2A receptor (5-HT2AR). Although known to inhibit 5-HT2AR mediated G protein coupling cascades, clozapine induces both internalization of the receptor and 5-HT2AR-mediated phosphorylation of Akt. Previously, we have demonstrated that serotonin also induces 5-HT2AR trafficking and Akt phosphorylation, events which depend upon interactions between the receptor and the intracellular scaffolding and regulatory protein beta-arrestin2. Moreover, we have demonstrated that the beta-arrestin2/5-HT2AR-mediated signaling pathway is involved in serotonin-induced, 5-HT2AR-mediated behavioral responses in mice.

Methods: Herein, we assessed whether beta-arrestin2 regulates clozapine's actions at the 5-HT2AR and whether such interactions are integral for clozapine's behavioral effects in mice. We determined clozapine mediated beta-arrestin2 translocation to the 5-HT2AR by both the DiscoveRx PathHunter beta-arrestin translocation assay and confocal microscopy and utilized mouse embryonic fibroblasts that lack both beta-arrestin1 and beta-arrestin2 to determine 5-HT2AR internalization in the absence of beta-arrestins. The dependence of beta-arrestin2 in the activation of Akt was determined in primary cortical neurons generated from the frontal cortex of neonatal beta-arrestin2 knock-out (barr2-KO) mice. Finally, the role of beta-arrestin2 in the behavioral effects of clozapine was also determined by assessing its ability to suppresses MK-801 and PCP-induced hyperlocomotion in barr2-KO mice.

Results: We find that unlike serotonin, clozapine does not induce interactions between the 5-HT2AR and beta-arrestin2, nor does it require beta-arrestins to promote the internalization of the receptor. In primary cortical neurons, clozapine-induced Akt phosphorylation is mediated by the 5-HT2AR, but unlike serotonin, it does not require beta-arrestin2 to facilitate this signaling event. Finally, clozapine's ability to suppress MK-801 or PCP-mediated hyperlocomotion is unaffected by the absence of beta-arrestin2.

Conclusions: These results demonstrate that while clozapine induces some similar receptor mediated events as serotonin, such as 5-HT2AR internalization and 5-HT2AR-mediated Akt phosphorylation, it utilizes unique signaling mechanisms to do so. The further elucidation of these mechanisms *in vivo* may allow for the development of more effective atypical antipsychotic drugs.

Keywords: clozapine, serotonin 2A receptor, arrestin, GPCR regulation, cellular signaling
Disclosure: C. Schmid, Nothing to Disclose; J. Streicher, Nothing to Disclose; L. Bohn, Nothing to Disclose.

T164. Cannabinoid Facilitation of Extinction Recall via Increased Recruitment of Prefrontal-hippocampal Circuitry in Healthy Humans

Christine A. Rabinak*, Mike Angstadt, Chandra Sripada, Mohammed R. Milad, Israel Liberzon, K. Luan Phan

University of Michigan, Ann Arbor, Michigan

Background: Enhancing extinction learning may optimize gains achieved by exposure therapy for anxiety disorders (e.g., maintenance of effects, hastened pace of improvement, greater generalization outside therapeutic context). Emerging evidence from animal studies suggest that enhancing cannabinoid system within the ventromedial prefrontal cortex (vmPFC) and hippocampus (HPC), brain structures critical to fear extinction, enhances fear extinction and its retention. However, the role of cannabinoids on the retention of extinction memory and its effect on the underlying neural circuits in humans remains unknown.
Methods: We conducted an fMRI study using a randomized, double-blind, placebo-controlled, between-subjects design, coupled with a standard Pavlovian fear extinction paradigm and simultaneous skin conductance response (SCR) recording with an acute pharmacological challenge with oral dronabinol (synthetic Δ^9−tetrahydrocannibinol; THC, n = 15) or placebo (PBO, n = 15) 2 hours prior to extinction learningin healthy adult volunteers to assess the effects of THC on vmPFC and HPC activation when tested for recall and maintenance of extinction learning at 24 hours and 1 week after training, respectively.
Results: Compared to subjects who received PBO, those who received THC showed increased vmPFC activation and functional coupling with the HPC, as well as low SCR to a previously extinguished CS when extinction memory recall was tested, suggesting that THC prevented the recovery of fear via increased recruitment of the vmPFC and HPC.
Conclusions: These results advance the neurobiology of extinction learning and prompt development of novel pharmacological modulators of the cannabinoid system to maximize the potency of exposure therapy for anxiety disorders.
Keywords: cannabinoid, extinction, fMRI, anxiety
Disclosure: C. Rabinak, Nothing to Disclose; M. Angstadt, Nothing to Disclose; C. Sripada, Nothing to Disclose; M. Milad, Nothing to Disclose; I. Liberzon, Nothing to Disclose; K. Phan, Nothing to Disclose.

T165. Detecting Disease-specific Differences in Mitochondrial Morphology and Distribution in Fibroblasts from Patients with Bipolar, Schizophrenic, and Major Depressive Disorders

Donna L. McPhie*, David Logan, Laura Sargent, John-Thomas Berry, Caitlin Ravichandran, Anne Carpenter, Bruce Cohen

McLean Hospital and Harvard Medical School, Belmont, Massachusetts

Background: A growing number of postmortem, brain imaging and genetic studies suggest that mitochondrial dysfunction may play a key role in the pathogenesis of mood and psychotic disorders. Mitochondria are the main energy producing units of the cell and exist in elaborate networks that allow for the accurate production and distribution of energy, as well as chemical signaling in critical regions, e.g. active synapses. Previously we identified changes in size and distribution of mitochondria in a sample of peripheral cells and brain tissue from affected Bipolar Disorder (BD) patients as compared to age-matched controls. We now extend these studies to larger sets of fibroblast samples generated by our laboratory from a clinically well-characterized group of patients exhibiting BD, Schizophrenia (SZ), Major Depressive Disorders (MDD) or age-matched clinically healthy control subjects (HC). In this study we examine mitochondrial morphological and distributional differences with both conventional directed measures and with unbiased machine learning.
Methods: Fibroblast samples from patients with either BD (n = 25), SZ (n = 25), MDD (n = 10) or age-matched controls (n = 25) were stained for mitochondrial, cytoskeletal and nuclear markers and imaged in three channels under a fluorescent microscope. Hundreds of features in each cell are measured using CellProfiler (Broad Institute). The directed measures of area, perimeter, form factor, center of gravity and radial distribution were selected for analysis, based on prior findings. In addition we used machine learning as an unbiased method to examine potential differences between cells using hundreds of features.
Results: Both approaches, directed measures and machine learning, indicate that mitochondrial features may vary with clinical presentation. Preliminary evidence from the directed measures analysis on a new set of samples shows differences in center of gravity measure in the SZ vs other groups, and radial distribution measures also show trends toward disease specific differences in the BD, SZ and control groups. The smaller sample of MDD vs control samples indicates trends toward differences in all of the directed measures analyzed. Additionally, machine learning on a small subset of mitochondrial objects revealed sets of features that classified each patient group separately, as well as a preliminary trend to predict the proper classification of a test set of patients among the BD, SZ and control groups.
Conclusions: The mitochondrial abnormalities observed may have broad implications for cell function in patients with psychiatric conditions and especially for cell function in brain, which requires ten times the energy production of the body on average. Sufficiently strongly associated markers of these diseases, identified by machine learning or directed measures on images from patient fibroblasts, could form the basis for novel clinical diagnostic tests. Importantly, morphological markers that can be detected in patient fibroblasts can be used for *in vitro* focused mechanistic studies of factors underlying the abnormalities. Also, cell systems could be used in testing for response to known therapeutics, and ultimately in screens to identify genetic modulators and novel therapeutic small molecules.
Keywords: mitochondria, bipolar disorder, schizophrenia, single cell image analysis
Disclosure: D. McPhie, Nothing to Disclose; D. Logan, Nothing to Disclose; L. Sargent, Nothing to Disclose; J. Berry, Nothing to Disclose; C. Ravichandran, Nothing to Disclose; A. Carpenter, Nothing to Disclose; B. Cohen, Nothing to Disclose.

T166. Emotional Processing Changes in Depressed Patients Following Antidepressant Treatment: an fMRI Study

Sidney Kennedy*, Sakina Rizvi, Jakub Konarski, Jonathan Downar, Roger McIntyre, Tim Salomons

University of Toronto, Toronto, Ontario, Canada

Background: Deficits in the identification of the emotive value of a stimulus, the production of affective states, and the regulation of affective states have been consistently reported in depression The aim of this study was to investigate differences between MDD and healthy controls in neural correlates of emotional processing and and to examine the effects of treatment on emotional processing circuitry by separately examining responders ($\geqslant$50% decrease in HAMD-17 score) and non-responders within the MDD group.
Methods: MDD subjects (n = 21) and age matched healthy controls (n = 18) were recruited to undergo functional magnetic resonance imaging (fMRI) while viewing positive, neutral, and negative pictures from the International Affective Picture System (IAPS). Scanning was done on all participants at baseline and 6 weeks. The MDD subjects received a 6-week trial of fluoxetine/olanzapine combination.

Results: At baseline MDD subjects exhibited increased activation compared to healthy controls in response to both positive and negative pictures (Positive: subgenual cingulate, prefrontal cortex; Negative: occipital cortex, precuneus, cuneus). Subsequent analyses showed baseline non-responders had decreased activity while viewing positive pictures in the posterior cingulate gyrus (BA 30) and precuneus compared to responders. Non-responders also had decreased activity while viewing negative pictures in the premotor cortex, and periaqueductal gray compared to responders; however, they demonstrated increased activity in the bilateral insula. Over 6 weeks, there were no significant within group (MDD, HC) or between-group changes in activation with positive images. In contrast, both MDD subjects and healthy controls demonstrated decreased activation to negative pictures, however the only significant between group difference was increased activity in the sensory cortex and motor cortex in MDD subjects compared to healthy controls. Within the MDD group, there was a positive correlation between reduced depression (HAMD-17 total scores) and reduced activation in the insula, and BA40/sensory cortex.
Conclusions: This study demonstrates differences in neural activation between responders and non-responders at baseline, which could indicate potential biomarkers for treatment response. Furthermore, successful treatment induces attenuated neural activity in response to negative pictures.
Keywords: major depression; fMRI; emotional processing; biomarkers
Disclosure: S. Kennedy, **Part 1:** SHK has received honoraria from AstraZeneca, Bristol-Meyers Squibb, Lundbeck, Pfizer, Servier, Spimaco, and St. Jude Medical, **Part 4:** SHK has received grant funding from Bristol-Meyers Squibb, Clera Inc, Lundbeck, and St. Jude Medical; S. Rizvi, **Part 1:** SJR has received travel funding from Eli Lilly and St. Jude Medical; J. Konarski, Nothing to Disclose; J. Downar, **Part 1:** JD received honoraria from Lundbeck; R. McIntyre, **Part 1:** RSM has reived honraria or travel funding from AstraZeneca, Bristol-Meyers Squibb, Eli Lily, France Foundation, GlaxoSmithKline, Janssen-Ortho, Lundbeck, Pfizer, and Shire, **Part 4:** RSM has received grant funding from AstraZeneca, Eli Lilly, Janssen-Ortho, and Shire; T. Salomons, Nothing to Disclose.

T167. Appraisal of Immediate and Delayed Reward is Impaired with Amygdalar-striatal Abnormalities in Pediatric Bipolar Disorder

Alessandra M. Passarotti*, Minjie Wu, Aneesh Nandam, Mani Pavuluri

University of Illinois at Chicago, Chicago, Illinois

Background: The aim of the present fMRI study was to examine possible dysfunction of reward circuits as they interface with affective and decision-making circuits in adolescents with pediatric bipolar disorder (PBD) relative to healthy controls (HC). In addition to affective dysregulation children with PBD exhibit deficits in reward-related processes associated with impulsivity, risk taking, low frustration tolerance, and altered responses to reward or punishment (Passarotti et al., 2010; Passarotti and Pavuluri, 2011; Rich et al., 2005; Gorrindo et al., 2005). To date we know very little on the neural mechanisms underlying these deficits that alter motivation and hinder reward-based interventions in PBD. To fill this gap this study examines the interface of reward-processes and impulse control in PBD during an ER-fMRI delay discounting task involving reward-based temporal decision-making. We hypothesized that relative to HC the PBD group would exhibit a greater behavioral bias for immediate reward, accompanied by altered neural response to immediate and delayed rewards in amygdala, ventral striatum, and lateral prefrontal regions.
Methods: Participants.* Twelve euthymic adolescent patients with PBD and 14 HC subjects (mean age 14.63 ± 1.6) participated in this study. All participants were matched for IQ and demographic measures. Task and fMRI session*. Participants underwent an 8 min Delay Discounting Task. On each trial two boxes appeared for 3500 ms, one with the word "today" and one with the word "later", each with a $ amount underneath, and they chose either the immediate reward or the delayed reward by pressing either of two response buttons. There were four possible time temporal delays (ranging from 3 to 30 days) and four possible reward amounts (ranging from $5 to $20), with all possible combinations presented with equal probability and randomly intermixed. The delayed reward was always a bigger amount relative to the immediate reward. Inter-trial interval was jittered (ranging from 2000 to 4000 ms). fMRI data acquisitions*. We performed gradient-echo echo-planar imaging (EPI) using a 3 Tesla whole-body GE scanner at the MR Center within the UIC Hospital (TR = 1.2 sec, TE = 25.4 ms, flip angle = 82, 23 axial slices, 1 NEX, 64x64 acquisition matrix, FOV = 20X20 cm2, 4 mm slice thickness, 3.1 mm in plane resolution, 1 mm gap). Anatomical images were also acquired in the axial plane (three-dimensional spoiled gradient recalled, 1.5 mm thick contiguous axial slices) and were later co-registered with the functional data. fMRI Data Analyses*. After motion correction and de-trending using FIASCO, the functional images were pre-processed with SPM5. Slice timing correction was applied to the data to remove signal variation due to slice acquisition temporal onset differences. The first functional image volume of each participant was used to determine parameters for spatial normalization into Montreal Neurological Institute (MNI) standardized space employed in SPM8 using non-linear transformation. The normalization parameters determined for the first functional volume were subsequently applied to all of the functional image volumes for each participant. The normalized functional images were then smoothed with an 8-mm full-width at half-maximum Gaussian filter. An ANOVA was run using SPM8. Significant clusters were thresholded at $p < 0.001$ uncorrected in the F-contrast map, and *t*-tests examined within- and between group differences for the immediate and delayed reward choice.
Results: As predicted the PBD group chose the immediate reward more frequently than HC ($p < .05$). When comparing activation for the immediate relative to the delayed reward choices, the PBD group exhibited no significant differences in activation in ventral striatum, amygdala, or prefrontal regions, suggesting poor differential appraisal of immediate and delayed rewards. On the contrary in HC delayed reward choice relative to immediate reward choice engaged more the bilateral ACC, suggesting increased cognitive control, but also more the right amygdala and bilateral ventral striatum, suggesting attribution of positive value to delayed rewards in HC. When directly comparing the two groups, dysfunction of amygdalar-striatal circuits emerged in PBD relative to HC both for immediate and delayed reward choices. For the immediate reward choice we found that PBD exhibited greater activation than HC in bilateral posterior cingulate regions and right amygdala, indicating greater affective processing and reactivity, but reduced activation in bilateral dorsal striatum, indicating poor cognitive modulation of decision-making. For the delayed reward choice PBD relative to HC showed decreased activation in both dorsal and ventral striatum and left amygdala, possibly indicating reduced sensitivity to delayed gratification in PBD patients.
Conclusions: While preliminary, the present fMRI findings are among the first to provide evidence of amygdala and striatal abnormalities associated with altered appraisal of immediate and delayed rewards in PBD. When choosing immediate reward PBD relative to HC exhibited greater amygdala activation and reduced dorsal striatum activation, whereas when choosing a delayed reward PBD relative to HC showed decreased activation in both dorsal and ventral striatum and amygdala. Future investigations of the neurobiological mechanisms underlying dysfunctional reward circuits and how they relate to poor affective and cognitive regulation in PBD will inform better diagnoses and interventions.
Keywords: pediatric bipolar disorder reward delay discounting amygdala striatum fMRI
Disclosure: A. Passarotti, Nothing to Disclose; M. Wu, Nothing to Disclose; A. Nandam, Nothing to Disclose; M. Pavuluri, Nothing to Disclose.

T168. Depressed Adolescents Show Less Enhancement of Positive Affect and Weaker Fronto-striatal Connectivity while Recalling a Positive Experience

Dana L. McMakin*, Jennifer Silk, Thomas Olino, Ronald Dahl, Kyung Hwa Lee, Erika E. Forbes, Neal Ryan, Greg Siegle

University of Pittsburgh, Pittsburgh, Pennsylvania

Background: Depression involves disruptions in aspects of positive affect and appetitive behavior; however, the nature of disruptions is only beginning to be understood. Enhancing and sustaining positive affective states helps to guide appetitive behavior and, in certain contexts, is essential to adaptive functioning. Recent work with depressed adults suggests difficulty sustaining positive affect responses to positive picture or film cues (i.e. reduced duration of self-report of emotion paralleled by reduced sustainability of reward-related striatal activation and fronto-striatal connectivity). These deficits may be particularly relevant to adolescence as neural circuitry (i.e. fronto-striatal circuitry) involved in enhancing and sustaining positive affect undergoes dramatic maturational change that is paralleled by escalating rates of depression. A deeper understanding of positive affect in adolescent depression may reveal novel targets for early intervention that can offset problems before they become entrenched. The current study examines neural and behavioral responses to enhancing and sustaining positive affect among adolescents with depression. We use a novel task with highly self-relevant stimuli to capture typical affective experiences of adolescents.
Methods: Forty-nine adolescents (ages 9-17; Mean = 14.3, SD = 2.18) participated in this study, including 25 (18 female) who were typically developing (healthy control) and 24 (18 female) who had a diagnosis of Major Depressive Disorder. Youth were first asked to generate a narrative regarding a recent positive life experience. Next, while completing an fMRI scan, they were told to try to get in a positive mood by re-experiencing and replaying their personal script in their mind, and listening to music they had identified as making them feel happy. Youth also used a computer mouse to continuously rate their affective experience on a 1 to 9 scale from very negative to very positive. The task included one 5-minute block. Neuroimaging data were collected using a 3.0 Tesla Trio MRI Scanner. Twenty-nine axial slices (3.2 mm isotropic voxels) were acquired every 1.5 seconds parallel to the AC-PC line using a T2* weighted reverse EPI pulse sequence (TR = 1500 ms, TE = 25 ms, FOV = 24 cm, flip = 72). Using independent *t*-tests we compared groups on self reported positive affect (mean and peak ratings across 5 minutes for data acquired at the level of seconds), and on indices of functional relations (zero-order correlation) using nucleus accumbens (associated with positive affect/reward responding) as a seed region for whole brain analysis.
Results: Youth with depression reported lower average (Depressed Mean = 7.18, SD = 1.24; Control Mean = 7.85, SD = .98; $t(47) = 2.06$, $p < .05$) and peak (Depressed Mean = 8.68, SD = 1.4; Control Mean = 9.34, SD = .79, $t(47) = 2.04$, $p < .05$) positive affect across the 5-minute task (See Figure 1), but there was no difference in sustainability of this response as assessed by a first versus second half difference score as well as a slope estimate. Functional connectivity analyses revealed lower functional relations between nucleus accumbens and areas of the ventromedial prefrontal cortex (vmpfc) (involved in self-relevant processing and affect regulation) in the depressed group relative to control participants ($t(46) = 4.21$, $p < .005$, 20 voxel contiguity threshold; see Figure 2). There was no indication of weaker sustainability in connectivity as assessed by first versus second half contrasts. Self reported positive affect (mean levels) was modestly related to nucleus accumbens-vmpfc connectivity indices ($p < .025$).
Conclusions: Relative to healthy youth, depressed youth showed less enhancement of positive affect (average and peak ratings) when asked to get in a positive mood by recalling a recent positive life experience. This was paralleled by indices of decreased fronto-striatal connectivity (nucleus accumbens and vmpfc), which is associated with positive affective and self-relevant processing. Future work may consider 1) if problems with enhancing positive affect predict problems with appetitive behavior and reward-related learning, 2) if intervention can improve enhancement of positive affect and related symptoms, and 3) if there are developmental windows when intervention strategies targeting key features of positive affect are particularly powerful and enduring due to enhanced neural plasticity in reward related circuits around the onset of puberty.
Keywords: depression, adolescents, development, affect, imaging, neuroscience
Disclosure: D. McMakin, Nothing to Disclose; J. Silk, Nothing to Disclose; T. Olino, Nothing to Disclose; R. Dahl, Nothing to Disclose; K. Lee, Nothing to Disclose; E. Forbes, Nothing to Disclose; N. Ryan, Nothing to Disclose; G. Siegle, Nothing to Disclose.

T169. Lipid Correlates of Antipsychotic-induced White Matter Changes in First-episode Psychosis

Philip R. Szeszko*, Delbert Robinson, Toshikazu Ikuta, Bart D. Peters, Juan A. Gallego, John Kane, Anil Malhotra

Feinstein Institute for Medical Research, Glen Oaks, New York

Background: There are limited *in-vivo* longitudinal data regarding the potential impact of antipsychotics on the brain white matter and how these changes may be associated with changes in lipid profiles. This may be a particularly important area for investigation given that a large proportion of cholesterol in humans is localized to the brain with the majority present in myelin.
Methods: In this study we investigated the effects of second generation antipsychotics on white matter integrity using tract-based spatial statistics (TBSS) in patients experiencing a first-episode psychosis with little or no prior antipsychotic exposure and their lipid correlates. Patients received diffusion tensor imaging exams and provided fasting serum lipid levels at the onset of antipsychotic treatment and then again following 12 weeks of treatment. Healthy volunteers received diffusion tensor imaging exams at a baseline timepoint and then again following 12 weeks. Thirty-five (26M/9F) patients (mean age = 21.5, SD = 4.6) experiencing a first-episode of psychosis and 35 (26M/9F) healthy volunteers (mean age = 21.8, SD = 4.8) participated in the study. Patients were treated, on average, for 12 weeks with either risperidone or aripiprazole in a double-blind randomized clinical trial.
Results: Patients demonstrated significant reductions in fractional anisotropy within parietal and occipital regions following antipsychotic treatment that survived family-wise error correction in TBSS. Greater fractional anisotropy reductions were associated with greater increases in cholesterol and greater increases in low density lipoprotein levels. No increases in fractional anisotropy were observed among patients following treatment. Moreover, no significant changes in fractional anisotropy were observed among healthy volunteers across the 12 week interval.
Conclusions: The results of our study suggest that reductions in fractional anisotropy, a putative measure of white matter integrity, are evident following approximately 12 weeks of atypical antipsychotic treatment. Fractional anisotropy reductions were relatively subtle (i.e., within the range of 3-4%) over the treatment trial and were most likely detectable through the use of a within subjects design, thus affording greater statistical power compared to cross-sectional studies. Short-term antipsychotic treatment may be associated with a subtle loss in brain white matter integrity that is related to worse lipid profiles.
Keywords: schizophrenia, diffusion tensor imaging, antipsychotics, white matter
Disclosure: P. Szeszko, Nothing to Disclose; D. Robinson, **Part 1:** Asubio Pharmaceuticals, **Part 4:** Bristol Myers Squibb, Janssen; T. Ikuta, Nothing to Disclose; B. Peters, Nothing to Disclose; J. Gallego, Nothing to Disclose; J. Kane, **Part 1:** Organon, Eli Lilly, BMS, Intracellular Therapeutics, Boehringer, Rules Based Medicine, Astra Zeneca, Otsuka, Novartis, Merck, Myriad, Esai, Pfizer, Lundbeck, J & J, Targacept, Shire, Amgen, Sunovion, Pierre Fabre, Janssen, Alkermes, Jazz, Forest Labs, **Part 2:** BMS, Otsuka, Merck,

Novartis, Lilly, MedAvante; A. Malhotra, **Part 1:** Genomind, Shire, Eli Lilly, Sunovion, Abbott, **Part 2:** Genomind, **Part 4:** Abbott.

T170. Depot-naltrexone Modulates Limbic Brain Activity and Reduces Smoking in Heroin Dependent Patients

Daniel D. Langleben*, Kanchana Jagannathan, Igor Elman, Catherine P. Koola, An-Li Wang, Shira Blady, Anna Rose Childress, Charles P. O'Brien

University of Pennsylvania, Philadelphia, Pennsylvania

Background: Relapse to drug use is the fundamental problem of addiction. Vivitrol, (Alkermes Inc, Cambridge, MA) is an injectable extended release formulation of naltrexone (XRNTX) that blocks opiate receptors for approximately one month after injection. Vivitrol is an FDA-approved treatment for opiate and alcohol dependence. In our recent studies (Langleben DD et al, 2012, Psychopharmacology 220:559-564, Langleben DD, Addict. Biol., In Press) an investigational XRNTX preparation (Depotrex, Biotek Inc) reduced drug craving and amygdala response to drug cues and potentiated medial prefrontal response to drug cues. The brain response was correlated with plasma levels of 6-beta-naltrexol. We hypothesized that Vivitrol treatment will be associated with similar brain and behavioral response to drug-related audiovisual cues.

Methods: In an ongoing study, eleven recently detoxified individuals (5F) with a history of daily heroin use, underwent brain functional Magnetic Resonance Imaging (fMRI) at 3 Tesla during exposure to audiovisual heroin related cues (AVC), immediately before (PRE) and two weeks after (ON) the first dose of Vivitrol. Subjective craving to opioids was assessed before and after cues exposure. Opioid, alcohol, cocaine, tobacco and marijuana use were assessed weekly with Time-Line Follow Back (TLFB) instrument. Ten of the participants were daily tobacco cigarette smokers.

Results: Baseline cue-induced heroin craving was significantly reduced ON XRNTX compared to baseline, with main effects of Session (PRE-XRNTX, ON-XRNTX) ($p<0.004$, $F=14.17$,$df=9$) and Condition (before and after fMRI heroin cues session, $p<0.007$, $F=11.93$,$df=9$). Paired *t*-tests showed reduced fMRI signal in the bilateral hippocampus and increased signal in the ventral striatum ($p<0.05$, $Z=1.64$,$df=9$). An unanticipated finding was the significant decrease in the self-reported number of cigarettes smoked daily ($p<0.03$) from 17 ($SD=12$) before XRNTX to 11 ($SD=8$) during XRNTX.

Conclusions: Vivitrol modulates the corticolimbic brain response to drug cues in opiate-dependent patients and reduces craving for heroin. Vivitrol may also reduce tobacco cigarette consumption in patients co-morbid for nicotine and heroin dependence. The analysis of the relationship between these neuroimaging data and behavioral and pharmacological data is ongoing. If confirmed in a full sample, our findings could form the basis of fMRI-guided treatment planning and monitoring in XRNT treatment of opiate dependence and further study of the potential efficacy of Vivitrol in the treatment of patients comorbid for opioid and nicotine dependence.

Acknowledgements: Supported by NIDA 5R01-DA024553-05 and supplemental funding under NIDA U.S. – Netherlands Bi-National Collaborative Research on Drug Abuse NOT-DA-10-018. Study medication provided free of charge by Alkermes, Inc.

Keywords: naltrexone, functional magnetic resonance imaging, heroin, opiate, Vivitrol

Disclosure: D. Langleben, **Part 4:** Investigator-sponsored agreement with Alkermes, Inc, Cambridge, MA, providing medication for the study reported here free of charge; K. Jagannathan, Nothing to Disclose; I. Elman, Nothing to Disclose; C. Koola, Nothing to Disclose; A. Wang, Nothing to Disclose; S. Blady, Nothing to Disclose; A. Childress, Nothing to Disclose; C. O'Brien, **Part 4:** Investigator Sponsored Agreement with Alkermes, Inc (Cambridge, MA)

T171. Dopamine Activity and Reward Processing in Smokers before and after Smoking Cessation: Combined [18F]FDOPA/fMRI Studies

Lena Rademacher, Susanne Prinz, Katja N. Spreckelmeyer, Oliver Winz, Jörn Schmaljohann, Felix Mottaghy, Ingo B. Vernaleken, Gerhard Gründer*

RWTH Aachen University, Aachen, Germany

Background: Research on nicotine addiction indicates greater ventral striatal activity in smokers compared to non-smokers in response to smoking-associated cues but blunted reactivity to non-drug rewards (David et al., Biol Psychiatry 2005; Martin-Soelch et al., Eur J Neurosci 2003). Furthermore, the only available small PET study on dopamine synthesis capacity in nicotine-dependent subjects demonstrated a substantial increase in [^{18}F]FDOPA uptake in the striatum in smokers compared to non-smokers (Salokangas et al., Am J Psychiatry 2000). It is completely unexplored, however, whether reward processing and dopamine metabolism change after smoking cessation. Therefore, the aim of the present study was to examine dopamine metabolism, neural correlates of reward anticipation and cue reactivity in non-smokers and nicotine-dependent smokers before and three months after smoking cessation in a combined [^{18}F]FDOPA/fMRI paradigm.

Methods: Nineteen smokers and 20 non-smokers performed two paradigms on a 1.5 T MR scanner: Monetary and social reward anticipation were investigated using the Monetary and Social Incentive Delay task (Knutson et al., Neuroimage 2000; Spreckelmeyer et al., SCAN 2009). The second paradigm examined cue reactivity by presenting blocks of smoking-related, neutral or sexually arousing pictures. Secondly, all subjects underwent a first [^{18}F]FDOPA PET scan including arterial plasma sampling and metabolite detection (acquisition time: 124 mins). All smokers took part in a smoking cessation course. From the total of 19 smokers, nine subjects succeeded in staying abstinent for at least three months; those subjects underwent a second fMRI scan with the same paradigms and a second [^{18}F]FDOPA PET scan. fMRI data were analyzed with SPM. The PET dynamic data were analyzed according to the "inlet/outlet-model" proposed by Kumakura et al. (JCBFM 2005) to obtain the net blood/brain clearance of [^{18}F]FDOPA (K), its total distribution volume (Vd), and the elimination rate of [^{18}F]fluorodopamine and its desaminated metabolites (k_{loss}) in striatum and midbrain.

Results: During both monetary and social reward anticipation smokers showed weaker BOLD activity of the NAcc compared to non-smokers. However, in response to smoking-associated pictures stronger neural responses were found in the caudate nucleus. For both paradigms no effect of smoking cessation could be detected. Preliminary analysis of the baseline PET data revealed a significant decrease in K values in the nucleus accumbens in smokers (mean = 0.016 ml/ccm/min) compared to non-smokers (mean = 0.0175 ml/ccm/min) at baseline. K values were also reduced in the caudate nucleus as a whole (smokers: 0.0148 ml/ccm/min; non-smokers: 0.0168 ml/ccm/min).

Conclusions: Our data implies that striatal activation during anticipation of non-smoking rewards is decreased in smokers while reactivity is increased for smoking-associated pictures. Contrary to previous findings, our PET data indicate that smoking is associated with reduced dopamine synthesis capacity rather than an elevation. The findings further suggest that neural activation during reward processing is not affected by smoking cessation. Analysis of the follow-up PET data is currently being performed. Together with the fMRI data, it will allow for a definite conclusion, whether the dysfunction of the reward system in nicotine-dependent smokers is long-lasting and persistent in nature.

Keywords: positron emission tomography, functional magnetic resonance, nicotine dependence, dopamine, reward

Disclosure: L. Rademacher, Nothing to Disclose; S. Prinz, Nothing to Disclose; K. Spreckelmeyer, Nothing to Disclose; O. Winz, Nothing to Disclose; J. Schmaljohann, Nothing to Disclose; F. Mottaghy, Nothing to Disclose; I. Vernaleken, Nothing to Disclose; G. Gründer, **Part 1:** Astra Zeneca, Bristol-Myers Squibb, Cheplapharm, Eli Lilly, Johnson & Johnson, Lundbeck, Otsuka, Servier, **Part 2:** Bristol-Myers Squibb, Cheplapharm, Eli Lilly, **Part 4:** Alkermes, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson.

T172. Functional Connectivity during Reward Processing in Adolescents with Bipolar I Disorder

Manpreet K. Singh*, Ryan G. Kelley, Erica Marie Sanders, Meghan Howe, Ian Gotlib, Kiki Chang

Stanford University School of Medicine, Menlo Park, California

Background: We previously examined reward functioning in youths soon after they experienced their first episode of mania and found BD youth to have reduced activations after priming in the subgenual anterior cingulate cortex (sACC) during reward anticipation. The aim of this study was to evaluate patterns of functional connectivity during reward processing in adolescents with bipolar (BD) and healthy controls (HC), hypothesizing that adolescents with BD will exhibit aberrant functional connectivity between the sACC and key subcortical regions involved in reward processing and emotion regulation while anticipating rewards during a monetary incentive delay (MID) task.
Methods: Adolescents (ages 13-18 years) with bipolar I disorder (BD, $N = 24$) were recruited by referral to the Stanford University Pediatric Bipolar Disorders Clinic and the surrounding community along with age and gender matched healthy children (HC, $N = 24$) without any psychiatric diagnosis. Diagnoses were determined by the Washington University in St. Louis Kiddie-Schedule for Affective Disorders and Schizophrenia (Geller et al. 1996) with established interrater reliability (kappa > 0.9). BD subjects were permitted to continue any pre-existing pharmacological interventions. Subjects were given a standardized monetary incentive delay (MID) computerized task measuring reward processing with an antecedent mood induction, and symptom severity ratings of mania using the Young Mania (YMRS). During the task, participants were cued to anticipate and respond to a rapidly presented target to gain or avoid losing varying amounts of money. Functional magnetic resonance images (fMRI) were acquired with a 3T GE Signa scanner using a standard whole-head coil (General Electric, Milwaukee) and high-resolution, T1-weighted, spoiled GRASS images. A psychophysiological interaction (PPI) analysis, as implemented in SPM8, was used to evaluate functional connectivity between the sACC and the rest of the brain. The deconvolved activation time courses from the seed ROI was multiplied by a block vector representing the contrast of interest, anticipation of gain > nongain. The individual model contained regressors for the interaction, the seed region time course, the original conditions, and motion regressors. The regressors were convolved with the canonical hemodynamic response function (HRF). The generated contrast images were then compared between BD and HC groups at a second-level random effects analysis. Two-sample *t*-tests were used to identify significant group differences of activation connectivity with the seed region. A significant PPI effect had a cluster-level threshold FWE corrected for multiple comparisons ($p < 0.05$) with a height threshold of $p < 0.01$ uncorrected and represents significantly higher connectivity between the seed regions and corresponding target regions during one condition (anticipation of gain) than another condition (anticipation of non-gain).
Results: After affective priming, BD youth relative to controls had increased functional connectivity between the sACC and the left caudate, right thalamus, right parahippocampal gyrus, right cerebellum, right lingual gyrus, right precuneus, left superior temporal gyrus, right fusiform gyrus, right superior parietal gyrus, and right angular gyrus during the anticipation of rewards.
Conclusions: Adolescents with bipolar I disorder show increased connectivity between the sACC and key striatal, thalamic, and subcortical regions while anticipating reward stimuli. These initial findings suggest differential recruitment of neural resources during reward processing based on group status. Correlations to clinical measures, connectivity patterns during anticipation of loss and feedback of reward and loss, and effects of medication exposure will be considered in future analyses. Further studies characterizing motivational, affective, and cognitive factors associated with mania are warranted to clarify the role of reward processing in the neurophysiology of pediatric BD.
Keywords: pediatric, bipolar, functional connectivity, subgenual anterior cingulate, reward
Disclosure: M. Singh, Nothing to Disclose; R. Kelley, Nothing to Disclose; E. Sanders, Nothing to Disclose; M. Howe, Nothing to Disclose; I. Gotlib, Nothing to Disclose; K. Chang, Nothing to Disclose.

T173. Greater MAO-A Binding in Borderline Personality Disorder: An [11C] Harmine PET Study

Nathan J. Kolla*, Alan A. Wilson, Sylvain Houle, Paul Links, Shelley McMain, Michael Bagby, Jeffrey H. Meyer

University of Toronto, Toronto, Ontario, Canada

Background: Borderline personality disorder (BPD) is found in 2% of the general population, 10% of psychiatric outpatients, and 20% of psychiatric inpatients. An important symptom of BPD is intermittent severe dysphoria, typically occurring in BPD inpatients, whereas BPD outpatients usually exhibit mild dysphoria. Monoamine oxidase A (MAO-A) is an enzyme that breaks down serotonin, norepinephrine and dopamine – chemicals that maintain normal mood. MAO-A levels are highly correlated with MAO-A activity. MAO-A V_T is an index of MAO-A level, and greater MAO-A V_T, especially in prefrontal and anterior cingulate cortex, occurs during dysphoric mood states, such as major depressive episodes, alcohol dependence, postpartum blues, and cigarette smoking withdrawal. In BPD, MAO-A levels are unknown. We hypothesized that MAO-A binding would be increased in BPD patients relative to healthy subjects, particularly in the prefrontal and anterior cingulate cortex, with the highest binding seen in BPD patients with severe dysphoria.
Methods: We scanned 19 female participants with BPD and 12 age- and sex-matched healthy participants using [^{11}C] harmine PET to measure MAO-A total distribution volume (MAO-A V_T). Thirteen of the BPD patients evidenced mild dysphoria, as indicated by Hamilton Depression Rating Scale (HDRS) scores of less than 24, while six BPD participants displayed severe dysphoria, indicated by HDRS scores of 24 or greater. Twelve of the BPD participants were medication-free, while seven were taking a psychotropic medication. Healthy participants had no history of mental illness and were medication-free. All participants were non-smoking and were not using illicit substances as determined by urine toxicology tests. MAO-A V_T was measured in the prefrontal and anterior cingulate cortex, caudate, putamen, ventral striatum, thalamus, hippocampus, and midbrain.
Results: MAO-A V_T was elevated in BPD as compared to the healthy state in the prefrontal and anterior cingulate cortices ($F_{2,28} = 11.2$, $p < .001$; elevated 27% and 19% in the prefrontal and anterior cingulate cortices, respectively). Within the BPD subjects, MAO-V_T was elevated in the severely dysphoric group as compared to the mildly dysphoric group in both the prefrontal and anterior cingulate cortex ($F_{2,16} = 5.9$, $p = .01$). Prefrontal and anterior cingulate cortex MAO-A V_T was increased by 45% and 37%, respectively, in severe dysphoric BPD compared to the healthy state.
Conclusions: Elevated MAO-A levels in the prefrontal and anterior cingulate cortex may reflect a mechanism to account for the dysphoria seen in BPD. Also, the relationship between state of BPD and MAO-A V_T

suggests that at least some of the neurobiology of BPD should be viewed as fluctuating in a manner similar to the symptoms of BPD. An implication for the treatment of BPD with severe dysphoria is that it may be important to consider developing therapeutics combining MAO-A inhibition with monoamine reuptake inhibitors.
Keywords: borderline personality disorder, monoamine oxidase A, positron emission tomography, harmine
Disclosure: N. Kolla, Nothing to Disclose; A. Wilson, Nothing to Disclose; S. Houle, **Part 1:** Research contracts with Eli Lilly, Bristol Myers Squibb, and SK Life Sciences, **Part 4:** Research contracts with Eli Lilly, Bristol Myers Squibb, and SK Life Sciences; P. Links, Nothing to Disclose; S. McMain, Nothing to Disclose; M. Bagby, Nothing to Disclose; J. Meyer, **Part 1:** Research contracts with Bristol Myers Squibb, SKLife, Eli-Lilly, Lundbeck, Takeda, and Mylan, **Part 4:** Research contracts with Bristol Myers Squibb, SKLife, Eli-Lilly, Lundbeck, Takeda, and Mylan.

T174. Developmental Trajectory of Sensory Cortical Gamma Synchrony Using Steady State Auditory Evoked Potentials

Raymond Y. Cho*, Christopher Walker, Nicola Polizzotto, Catherine Fissell, Thomas Wozny, Chi-Ming Chen

University of Pittsburgh, Pittsburgh, Pennsylvania

Background: Gamma synchrony disturbances in schizophrenia thought to underlie a wide range of sensory and cognitive processing impairments in the illness. Steady state auditory evoked potentials (SSAEP), an entrainment of EEG responses to a driving frequency, has reliably indexed such disturbances, particularly at 40 Hz, indicating that it may be a potential biomarker for the disorder. Given the developmental context of the disorder, it is important to gain an understanding of the normal developmental trajectory of SSAEPs from late childhood to early adulthood, the critical period for the emergence of psychosis.
Methods: Data from 175 participants, aged 8 to 22 years old and divided into five age bins of three years each, were collected with high-density EEG recordings during auditory click-trains presented at frequencies of 20, 30, and 40 Hz. EEG data were wavelet transformed to derive evoked power, intertrial coherence and cross-frequency coupling measures for the respective the driving frequencies.
Results: We found monotonic increases in power in the 40 Hz SSAEP in subjects 8 through 16 years of age, which then plateaued through late adolescence before decreasing in young adults. Intertrial coherence and gamma amplitude modulation by delta band phase tracked the increases in power until peaking in mid-adolescence before decreasing linearly through late adolescence and early adulthood. By contrast, the same measures for the 20 Hz SSAEP generally showed the opposite trends indicating frequency specificity of findings in the gamma band.
Conclusions: The observed Increases with age in neural synchrony measures for the 40 Hz SSAEP is consistent with the idea that there is an increasing ability of cortical circuits to support synchronous gamma oscillations over the period spanning childhood through mid-late adolescence. Decreases in the same measures over late adolescence and early adulthood may reflect late refinements in cortical development as suggested by parallel decreases in temporal cortical grey matter volumes over the same period. The relationship of our findings to developmental trajectories of critical neurobiological components that support gamma synchrony and their relevance to schizophrenia will be discussed.
Keywords: gamma synchrony development auditory schizophrenia
Disclosure: R. Cho, Nothing to Disclose; C. Walker, Nothing to Disclose; N. Polizzotto, Nothing to Disclose; C. Fissell, Nothing to Disclose; T. Wozny, Nothing to Disclose; C. Chen, Nothing to Disclose.

T175. Subgenual Cingulate Function in Borderline Personality Disorder and Major Depression

Brian J. Mickey*, Alexander Andrews, Chelsea Cummiford, Mary Heitzeg, Scott A. Langenecker, Tiffany Love, Benjamin J. Sanford, Kenneth Silk, Jon-Kar Zubieta

University of Michigan, Ann Arbor, Michigan

Background: The relationship between borderline personality disorder (BPD) and major depressive disorder (MDD) is controversial. Abnormalities of the subgenual anterior cingulate cortex (ACC) have been described in both disorders, but conclusions about the neurobiological relationship between BPD and MDD have been limited by the absence of neuroimaging studies examining both disorders with the same design.
Methods: We studied 21 women with BPD, 14 women with MDD, and 54 healthy control women, all medication-free. Hemodynamic responses were measured using functional magnetic resonance imaging with a task that contrasted negative and positive emotional words with neutral words. Task effects and functional connectivity were quantified. The subgenual ACC, medial prefrontal cortex, and amygdalae were examined as regions of interest.
Results: Subgenual ACC activation to negative and positive words was abnormally high for both BPD and MDD, and the two groups did not differ from each other. However, BPD and MDD groups were distinguished by the functional connectivity of subgenual ACC with amygdala, posterior cingulate, and visual cortex. The MDD group, but not the BPD group, had abnormally strong positive connectivity during the positive word (mood-incongruent) condition.
Conclusions: We found both shared and distinguishing subgenual ACC abnormalities in BPD and MDD. The disorders share in common a hypersensitivity to the emotional content of words, which may contribute to the high comorbidity between MDD and BPD. They are distinguished by the pattern of functional connectivity of subgenual ACC to other brain regions, which could underlie differences in clinical presentation.
Keywords: depression, personality disorders, fMRI, emotion, nosology
Disclosure: B. Mickey, **Part 1:** Dr. Mickey has received salary support from St. Jude Medical through a contract to the University of Michigan; A. Andrews, Nothing to Disclose; C. Cummiford, Nothing to Disclose; M. Heitzeg, Nothing to Disclose; S. Langenecker, Nothing to Disclose; T. Love, Nothing to Disclose; B. Sanford, Nothing to Disclose; K. Silk, Nothing to Disclose; J. Zubieta, **Part 1:** Dr. Zubieta has served as a paid consultant for Eli Lilly & Co., Johnson & Johnson, Merck, and Abbott for unrelated work.

T176. Chronic HDAC Inhibitor Treatment Alters Brain Glucose Metabolism in Rats: Examining 18F-flurodeoxyglucose Uptake with Positron Emission Tomography

Frederick A. Schroeder*, Michael Granda, Anna Cha, Chris Moseley, Stephen J. Haggarty, Jacob M. Hooker

Harvard Medial School / Massachusetts General Hospital, Boston, Massachusetts

Background: Epigenetic mechanisms involving chromatin-modifying enzymes and remodeling factors are increasingly implicated in the pathophysiology of psychiatric diseases, mood dysfunction and cognitive disorders. A central role of these epigenetic mechanisms involves transcriptional regulation through modification of chromatin – DNA packaged around octameric cores of histone proteins H2A, H2B, H3 and H4. Post-translational modification at N-terminal sites of core histone protein alters chromatin structure and modulates transcriptional activity. The most widely studied histone modification is lysine acetylation and is controlled by the histone deacetylase (HDAC) family of enzymes. Recent reports in rodent models using genetic disruption

or treatment with small molecule HDAC inhibitors draw attention to the Class I HDAC enzymes - HDAC 1, 2, 3 and HDAC8 - in describing an important role of HDAC activity in regulating manic-like hyperactivity, learning and memory, and mood-related behaviors. However, the interpretation of these findings is limited by: i) the use of HDAC inhibitors with limited specificity for Class I HDAC subtypes and ii) further examining brain regions *already implicated* in the disease/ treatment model. Further, despite the translational promise of such preclinical results, no study has yet paired chronic HDAC inhibitor treatment of animals with neuro-imaging by positron emission tomography – an imaging modality well-established in the clinical setting. To this end, we describe here our current findings using two selective HDAC inhibitor tool compounds from the literature to examine the impact of subtype selective HDAC inhibitor treatment on neural signaling in rats. In order to better understand the effects of these drugs throughout the brain, we used high resolution positron emission tomography (PET) and the established radiotracer, ^{18}F-flurodeoxyglucose (^{18}F-FDG), to investigate regional differences in brain glucose metabolism as an indicator of neural activity and circuitry.

Methods: Adult, male Sprague-Dawley rats (250-300g, n = 6-12/group) were treated for seven days via daily intraperitoneal (i.p.) treatment with i) vehicle (10% DMSO, 45% PEG-400, 45% saline), ii) a selective inhibitor of HDAC 1 and HDAC2 or iii) a selective inhibitor of HDACs 1, 2 and 3. One day after the first or last drug treatment, hypoglycemic rats (induced by 12hours food restriction) were administered the radiotracer glucose analog ^{18}F-FDG (1mCi +/−0.15mCi, i.p.). After one hour of ^{18}F-FDG uptake, brain glucose metabolism was imaged for 15 minutes by positron emission tomography (PET) followed by an anatomical computed tomography (CT) scan. Data were reconstructed using MLEM-3D, coregistered to anatomical scans and corrected for and injected activity and decay. Image quantification and statistical parametric mapping (SPM) was performed using PMOD software (v3.3, PMOD Technologies, Ltd, Zurich, Switzerland) and the SPM-5 software suite (University College London) for MATLAB (The MathWorks, Inc).

Results: We found, using SPM and region of interest analysis, that treatment with selective Class I HDAC inhibitors resulted in distinct patterns of ^{18}F-FDG uptake that were both robust (3-8% changes) and significantly different from vehicle-treated controls ($p < 0.05$). Increases in ^{18}F-FDG uptake were observed in the prefrontal cortex of HDAC-inhibitor-treated rats, consistent with the central role of this brain region in depression- and reward-related behaviors previously shown to be altered by Class I HDAC inhibitor treatment. Analysis also revealed that chronic HDAC-inhibitor treatment induced regional decreases in ^{18}F-FDG activity, demonstrating dynamic effects of histone modifying drugs on neural signaling. We confirmed, by Western immunoblotting of histone extracts from dissected rat brain, that treatment with selective HDAC inhibitors results in elevated histone acetylation one hour after the final treatment, compared to vehicle-treated controls. However, one day after the final dose, changes in histone acetylation of total chromatin did not strictly correlate with regional increases or decreases in ^{18}F-FDG uptake in brain.

Conclusions: These results represent the first study to examine the effects of chronic treatment with selective histone deacetylase inhibitors on brain glucose metabolism in rats. Our preliminary findings indicate that chronic inhibition of the Class I HDAC enzymes HDAC 1 and 2 or HDAC 1, 2 and 3 each results in unique activation and deactivation of neural signaling, and highlights potential treatment-related neural circuitry and under-studied brain nuclei. We interpret these ^{18}F-FDG significance and activity maps as an in-road to understanding the functional connectivity associated with selective HDAC inhibition. Ongoing work using novel selective inhibitors and established imaging tools will clarify the role of HDAC subtypes in neural signaling. Our findings provide evidence for brain regions that may harbor HDAC subtypes and enzyme activity crucial to the mechanism of psychiatric disease and treatment and further underscores the utility of PET imaging as a translational research tool.

Keywords: epigenetics, histone, rat, acetylation, glucose
Disclosure: F. Schroeder, Nothing to Disclose; M. Granda, Nothing to Disclose; A. Cha, Nothing to Disclose; C. Moseley, Nothing to Disclose; S. Haggarty, Nothing to Disclose; J. Hooker, Nothing to Disclose.

T177. Experimentally Delayed Puberty Interacts with Social Stress to Produce Widespread Effects on the Development of Brain White Matter Tracts and Behavior in Rhesus Monkeys

Jodi R. Godfrey*, Brittany Howell, Xiaodong Zhang, Govind Nair, Xiaoping Hu, Mark Wilson, Mar Sanchez

Emory University, Atlanta, Georgia

Background: Social stress during childhood and adolescence can result in alterations in hypothalamic-pituitary-adrenal (HPA) axis function and emotional regulation. Naturally occurring social subordination in rhesus macaque social groups serves as an ecologically relevant model of chronic social stress and we have shown that low ranking females show neuroendocrine signs of chronic stress (hypercortisolemia) and alterations in behavioral and brain structural development. In adult females estradiol (E2) has been shown to be important for mood regulation, as it targets a number of neurochemical systems responsible for emotional responses to social and environmental situations and is present in low levels prior to the onset of puberty. Because subordination stress delays puberty in females fed a typical low calorie diet, it is unknown whether social subordination affect brain maturation directly or whether the effects are due to low levels of E2 resulting from delayed puberty. The goal of this study was to determine if delaying puberty experimentally (via administration of a GnRH agonist, Lupron) interacts with social stress to alter the development of brain white matter tracts in females.

Methods: Using a longitudinal experimental design, DTI scans were collected on 45 socially housed juvenile female rhesus monkeys at 16-23 months of age (pre-puberty) and again at 26-33 (peri-puberty) months of age. 23 of these subjects received monthly injections of the GnRH analog, depot Lupron (Tap Pharmaceuticals) to experimentally delay the onset of puberty. DTI scans were collected using a single-shot dual spin-echo EPI sequence with GRAPPA (R = 3), voxel size: 1.3x1.3x1.3 mm3 with zero gap, 60 directions, TR/TE = 5000/86 ms, b:0, 1000 s/mm2, 12 averages. FSL software (FMRIB, Oxford, UK) was used for preprocessing. Fractional anisotropy (FA), a DTI measure of water diffusion directionality, was used as an index of structural integrity of tracts. FA is higher in myelinated axons/tracts because water diffusion is more restricted than unmyelinated tracts or other brain tissue, which do not have a strong directionality of water diffusion. DTI data was analyzed using tract-based spatial statistics (TBSS) in FSL software. TBSS is a tract-wise analysis approach where an average FA image from all subjects is created and registered into standard space, and then a skeletonized FA map is calculated by representing the center of white matter tracts present in all subjects. Each subject's FA data is projected onto the skeleton and this skeletonized FA data fed into AFNI software for statistical analysis to conduct a repeated measures ANOVA. Significance level for voxels with group differences was set at $p < 0.005$, followed by cluster correction (>150 contiguous significant voxels). Measures of stress physiology (basal and stress-induced levels of cortisol, in addition to social behavior of the juvenile females in their groups (aggression, submission, affiliation, play), as well as behavioral reactivity during the Human Intruder task (designed to evoke emotional responses to an unfamiliar human), including fear, aggressive, and submissive behaviors, as well as vocalizations were also collected and entered in a multiple regression model to examine functional correlates of the brain structural changes.

Results: There were widespread effects of Lupron treatment on brain white matter tract structural integrity (FA), including prefrontal, occipital, parietal, somatosensory, and temporal cortices white matter. There were also extensive Lupron effects in the brainstem and cerebellum white matter. A global analysis of

FA revealed an overall higher, although marginally significant ($p = 0.073$) white matter tract integrity in Lupron-treated than non-treated juvenile females. These effects indicate global effects of E2 levels during and even before puberty on the development of brain white matter tracts. There were also widespread effects of age, particularly in the anterior internal capsule, the thalamic bundle, the splenium of the corpus callosum, the cerebellum and the parietal and pre-frontal cortices white matter. No effects of social status were found at that high stringency p value; however, when the p value was lowered to $p = 0.05$, Subordinate animals showed higher white matter tract integrity than Dominants in temporal and parietal cortices. Lupron also had significant behavioral and neuroendocrine effects across the two ages studied, including reductions in affiliative and play behaviors during social behavior observations, and increased time sitting and playing alone, in comparison to non-Lupron treated controls. During the Human Intruder task, Lupron treated subjects averted their gaze from the intruder more often and for longer durations than do non-Lupron treated controls.

Conclusions: The results of this study have profound implications for female primate brain development because they suggest that estrogen is important for brain maturation even before puberty, and underscores the impact of advanced versus delayed puberty in girls. In fact, Lupron is prescribed to young girls for the treatment of precocious puberty. This nonhuman primate model provides evidence that even the low levels of pre-pubertal E2 have developmental effects on the brain and that depleting these low levels of E2 causes global, widespread changes on the development of white matter tracts. We are currently analyzing the functional correlations between the brain structural effects and the effects detected on behavior and stress physiology.

Keywords: Non-human Primate, Imaging, Development, Puberty, Estradiol

Disclosure: J. Godfrey, Nothing to Disclose; B. Howell, Nothing to Disclose; X. Zhang, Nothing to Disclose; G. Nair, Nothing to Disclose; X. Hu, Nothing to Disclose; M. Wilson, Nothing to Disclose; M. Sanchez, Nothing to Disclose.

T178. Regional Analysis of Naltrexone Effects on Mu-opioid Availability *in Vivo*

Chelsea Cummiford*, Tiffany Love, Robert Koeppe, Jon-Kar Zubieta

University of Michigan, Whitmore Lake, Michigan

Background: Naltrexone is commonly used to treat alcoholism and opiate addiction. Although naltrexone is a potent mu-opioid receptor antagonist, patient compliance to the medication is poor. Therefore, there is clinical value in the understanding of the duration of mu-opioid receptor blockade and whether regional differences in the brain exist. In this study, we examined the duration of opiate receptor blockade in healthy participants after 7 days of administration of a clinical dose of naltrexone.

Methods: Participants included eight healthy, non-smoking males, ages 20-31. Mu-opioid receptor availability was measured across four time points using positron emission tomography (PET) and the selective mu-opioid receptor radiotracer [11C] carfentanil. A baseline PET scan was performed before naltrexone administration. After 7 days of 50 mg/day oral doses of naltrexone, participants had 3 more PET scans: 2 hours, 1 day, and 2 days after the last dose of naltrexone. In addition, anatomical MRI scans were acquired for spatial coregistration with PET images and normalization to a standard space. Regions of interest included the nucleus accumbens (NAcc), amygdala, hippocampus (bilaterally) and the anterior cingulated. These regions were chosen because they are involved in reward processing, emotional regulation, and have been implicated in substance abuse, all areas in which the mu-opioid receptor is involved. Repeated measures ANOVA's were performed for the 3 time points after naltrexone administration.

Results: 2 hours after last dose of naltrexone, mu-opioid receptors were 93-94% blocked in the left and right NAcc, 95% and 93% in the left and right amygdala, 83% in the hippocampi and 90% in the anterior cingulate. 1 day after the last dose, left and right NAcc 87%-90%, left and right amygdala 89%, left and right hippocampus 79%, left anterior cingulate 86%, right anterior cingulate 85%. 2 days after the last dose: left and right NAcc 58%-62%, amygdalae 74-76%, hippocampi 79%-82%, anterior cingulate 74%. In a repeated measures ANOVA between 2 hrs, 1 day and 2 days after the last dose, significant differences ($p < .05$) were found between all time points in the left and right NAcc, with lesser effects in the amygdalae and anterior cingulate. There were no significant differences between any of the 3 time points after naltrexone administration in the hippocampus.

Conclusions: This study examined mu-opioid receptor availability *in vivo* after one week of naltrexone administration. After one week of a clinically relevant dose, naltrexone blocked ~90% of mu-opioid receptors in healthy participants. 1 day after the last dose, ~85% of receptors are still blocked, and 2 days after the final dose 72% of mu-opioid receptors remain blocked by naltrexone. However, some regional differences emerged in the extent of blockade, particularly in the NAcc. Given the difficulty of maintaining naltrexone treatment in substance abusing samples, the duration and extent of regional blockade needs to be considered in clinical trials, and may be relevant to its behavioral effects.

Keywords: Naltrexone, PET, mu-opioid, substance abuse

Disclosure: C. Cummiford, Nothing to Disclose; T. Love, Nothing to Disclose; R. Koeppe, **Part 1:** Johnson & Johnson, Eli Lily (Avid Radiopharmaceuticals), Merck; J. Zubieta, Nothing to Disclose.

T179. Multivariate Pattern Classification Reveals Distributed Effects of Oxycodone on the Resting Brain Connectome in Humans

Chandra Sripada, Daniel Kessler, Mike Angstadt, Robert C. Welsh, Scarlet Guo, K. Luan Phan*

University of Illinois at Chicago, Chicago, Illinois

Background: Oxycodone is a semi-synthetic opioid with potent agonist activity at mu, kappa, and delta receptors. Behavioral and clinical studies demonstrate that oxycodone reliably produces acute and chronic alterations in a number of neurocognitive functions including pain/nociception, motivation/reward, executive control, memory, and movement. While receptor-level effects of oxycodone have been well characterized, the mechanisms by which oxycodone impacts large-scale, distributed neural systems that underlie these neurocognitive functions are poorly understood. Intrinsic connectivity networks (ICNs) consist of distributed brain regions exhibiting coherent activity, and which are reliably detected from low-frequency oscillations of the blood oxygenation level dependent (BOLD) signal during the resting state. Convergent evidence indicates that ICNs constitute fundamental organizational elements of human neural architecture. Individual ICNs have been implicated in specific neurocognitive functions such as attention control and somatomotor processing. Moreover, aberrant connectivity within specific ICNs is linked to clinically-relevant symptom dimensions across psychiatric disorders. Thus investigating the impact of acute drug administration on resting state ICNs constitutes a powerful method to characterize the impact of pharmacological compounds on large-scale functional brain networks. Previous studies have investigated ICNs primarily with seed-based methods, which are restricted to investigating correlated activity with a single region at a time. The current study couples whole-brain connectomic imaging with multivariate pattern classification to comprehensively characterize distributed patterns of oxycodone effects on resting state connectivity across the entire brain.

Methods: In a within-subject, double-blind, randomized, cross-over design, 16 healthy individuals underwent three fMRI scanning sessions, each separated by approximately one week. In each scanning session, participants received either placebo (PBO),

10 mg oxycodone (low-dose oxycodone; L-OXY), or 20 mg oxycodone (high-dose oxycodone; H-OXY) 60 minutes prior to a six minute resting state scan. Our connectomic pattern classification analysis involved three major steps: *1) Connectome generation*: After standard pre-processing (slice-time correction, realignment, normalization, smoothing), connectomes were generated for each subject and session separately. A grid-based approach was utilized: 1080 4.35 mm radius spherical regions of interest (ROI) were placed at 12 mm intervals across the brain. The spatially–averaged BOLD time series was extracted from each ROI, and Pearson's correlations were calculated pairwise between each time series. Additional regressors controlled for motion and signal derived from white matter and cerebrospinal fluid. *2) Pattern classification*: A novel 'paired Support Vector Machine (SVM)' framework was implemented in order to account for the within-subject structure of the data (i.e., multiple scanning sessions from the same subject). SVM classifiers were trained separately to distinguish L-OXY versus PBO and H-OXY versus PBO. Univariate feature pruning was utilized and performance was assessed with {25, 50, 100, 500, 1000} retained features. Leave one out cross-validation was used to assess classifier performance, with feature pruning nested within the folds of the cross-validation to obviate bias. *3) Visualization*: For each trained classifier, we identified the set of edges that contributed to classification across every fold of the leave one out cross-validation ('the consensus discriminative connectome'). The network affiliation of the nodes associated with these edges was established according to the ICN parcellation scheme of Yeo and colleagues (2011).

Results: *L-OXY versus PBO*: Trained SVM classifiers achieved peak accuracy at 100 features (93.8% accuracy, $p < 0.001$ binomial test). The consensus discriminative connectome consisted of 51 edges. Of these, 31 edges involved the somatomotor network. Other networks that contributed multiple edges to the discriminative connectome included the default network (n = 8), cerebellum (n = 6), and frontoparietal networks (n = 5). *H-OXY versus PBO*: Trained SVM classifiers achieved peak accuracy at 50 features (86.7% accuracy, $p = 0.007$ binomial test). The consensus discriminative connectome consisted of 25 edges. Twenty-three of these edges exhibited positive connectivity under PBO, and H-OXY administration reduced connectivity in all these edges. Edges involving somatomotor (n = 11) and frontoparietal networks (n = 7) accounted for 18 of the 25 edges. Of note, no edges in the discriminative connectome for either L-OXY or H-OXY involved striatal regions.

Conclusions: We found that both low- and high-dose oxycodone produce reliable multivariate neural signatures that enable highly accurate classification of drug versus placebo. Low-dose oxycodone affects a wider set of regions—encompassing somatomotor, frontoparietal, default, and cerebellar networks—compared to high-dose oxycodone whose discriminative connectome involved fewer connections, and selectively encompassed somatomotor and frontoparietal networks. It is notable that neither dose of oxycodone affected connectivity with striatum, a region densely populated with opioid receptors. This suggests that oxycodone affects distributed cerebral regions through multiple pathways, at least some of which may be relatively independent of striatum. Overall, this study demonstrates the feasibility and utility of connectomic imaging coupled with multivariate pattern classification for delineating the effects of acute drug administration on distributed brain networks. Moreover, our findings regarding oxycodone effects on resting state connectivity networks invite translation to clinical disorders such as substance use disorders (e.g., opiate dependence) and chronic pain syndromes. **Funding:** This work was supported by a National Institute on Drug Abuse, R03DA024197 awarded to K. Luan Phan.

Keywords: oxycodone, resting state, connectomics, pattern classification, pharmaco-fMRI

Disclosure: C. Sripada, Nothing to Disclose; D. Kessler, Nothing to Disclose; M. Angstadt, Nothing to Disclose; R. Welsh, Nothing to Disclose; S. Guo, Nothing to Disclose; K. Phan, Nothing to Disclose.

T180. Effects of Levodopa-carbidopa-entacapone on Neural Responses to Cocaine-related Stimuli and Non-drug Rewards in Regular Cocaine Smokers

Gillinder Bedi*, Nehal P. Vadhan, Edward V. Nunes, Richard W. Foltin, Adam Bisaga

Columbia University College of Physicians and Surgeons, New York, New York

Background: Despite numerous preclinical and clinical trials of medications for cocaine dependence, no effective medication has been identified. One common target is dopaminergic (DA) neurotransmission, which is reduced in striatal regions in cocaine users relative to controls (Martinez and Narendran, 2010). Supporting this is recent evidence that treatment with the DA precursor levodopa (l-dopa) increases cocaine abstinence (Schmidt et al. 2008). Notably, this effect only occurred in combination with voucher-based contingency reinforcement therapy. Given the role of DA in reward prediction, reinforcement learning, and motivational processing, it is possible that enhanced DA neurotransmission specifically interacts with behavioral treatment to improve outcomes by increasing cocaine users' capacity to respond to non-cocaine rewards. The current data, collected as part of a laboratory study assessing the safety of the DA agent levodopa-carbidopa-entacapone (LCE) in combination with smoked cocaine, investigated the effect of LCE treatment on neural correlates of responses to cocaine-related stimuli and pictures of non-drug reinforcers in regular cocaine smokers.

Methods: Twelve healthy non-treatment seeking participants (11 male; 1 female: 21 to 50 years old) who reported smoking cocaine on average 3.8 (± 2.6) days/week and spending $164 (± 134) on cocaine weekly completed an 11-day inpatient study in which they received 4.5 days of LCE (titrated to the target dose of 400 mg/100 mg/200 mg BID) and 4 days of placebo, with 2 intervening placebo days for medication clearance. Dose order was counterbalanced and participants were blinded to medication condition. Once during the target LCE dosing phase and once during the placebo phase, participants underwent functional Magnetic Resonance Imaging (fMRI) while viewing and rating the valence of standardized cocaine-related pictures, pictures of positive non-drug stimuli (e.g. sex, food, social affiliation) and affectively neutral pictures. Following scanning, participants viewed the stimuli again, rating the subjective valence, arousal levels, and cocaine craving produced by each image. Behavioral results were analyzed using single sample *t*-tests, and paired *t*-tests assessing differences between ratings during placebo and LCE treatment. For fMRI data, contrasts specified at the first level (cocaine versus neutral pictures; positive non-drug versus neutral pictures) were analyzed at the second level using single-sample *t*-tests, or for differences between placebo and LCE conditions, paired *t*-tests.

Results: Under placebo, cocaine-related pictures were rated as producing higher cocaine craving than did the positive non-drug or neutral stimuli ($p = .01$); they were also rated as less pleasant than were the positive non-drug stimuli ($p < .05$). There was no effect of LCE on ratings of valence, arousal, or craving levels after viewing cocaine, positive non-drug, or neutral stimuli. Initial analyses of fMRI data indicate that on placebo, cocaine relative to neutral stimuli elicited activation in regions previously implicated in drug cue-responding including bilateral caudate, bilateral insula, and dorsal and anterior cingulate cortex. There was no effect of LCE on neural response to cocaine or positive-non-drug stimuli relative to neutral pictures.

Conclusions: Initial analyses do not support the hypothesis that enhancing DA neurotransmission with short-term LCE treatment increases behavioral or neural responses to non-drug reinforcers in this population. It is possible that differential response would have been observed in individuals receiving cocaine treatment. Ongoing research will assess the impact of maintenance on LCE on neural responses to drug and alternative reward related stimuli, as well as clinical outcome, in treatment-seeking cocaine users.

Keywords: drug abuse cocaine dependence medication dopamine reward processing
Disclosure: G. Bedi, Nothing to Disclose; N. Vadhan, Nothing to Disclose; E. Nunes, Nothing to Disclose; R. Foltin, Nothing to Disclose; A. Bisaga, Nothing to Disclose.

T181. Evocative Cues Trigger Limbic Motivational Circuits and Differentially Disrupt "Cognitive Control" in Real-time Functional Magnetic Resonance Imaging

Anna Rose Childress*, Jeremy Magland, Oscar Bartra,
Jessie Lupardus, Robert Fabianski, Shing Chun Lam, Kimberly Young,
Jesse Suh, Teresa Franklin, Daniel Langleben, Charles P. O'Brien

University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

Background: In 2005, deCharms et al. reported that real-time fMRI feedback training improved the control of chronic pain. This finding ignited hope that real-time fMRI feedback might be used to improve cognitive control over a wide variety of symptoms and states – including the cue-triggered drug motivation that fuels addiction relapse. Our long-term goal is to test whether real-time fMRI feedback can help cocaine patients maintain cognitive control *despite* encountering evocative drug cues. As a step toward this goal, we are testing whether visual cues (neutral, cocaine, and aversive) can disrupt cognitive control during a task that requires thought-shifting between distinct brain states (e.g., imagined spatial navigation or repetitive arm activity), vs. rest. We hypothesized that the disruptive effects of evocative drug cues depends on drug use history – e.g., that cocaine patients will be more vulnerable to disruption by cocaine cues, relative to other cue types, and relative to the effects of these same cues in healthy controls. We also predicted that evocative cues in both populations would trigger limbic motivational circuitry – helping to explain how these cues "de-rail" cognitive performance.
Methods: Classifier training (Cognitive control tasks): BOLD fMRI at 3T (Siemens; TR = 2sec) with a Partial Least Squares (PLS) linear classifier was used to characterize the whole-brain response for subjects (ongoing: current sample size, 21 healthy controls; 5 abstinent cocaine patients) during picture-assisted cognitive control tasks that involved alternations between an instructed brain state vs. Rest. Two tasks were used, to provide variety: One task featured on-magnet instructions to *navigate the scene on the screen* (6 sec, *"Put yourself in the scene"…*) v. Rest (6 sec). The other featured on-magnet instructions to *imagine playing the "arm" sport on the screen* (6 sec, "*Imagine hitting the ball over and over…")* v. Rest (6 sec). **Distractors:** After brief training ($\sim$ 2 minutes) to establish classifiers based on the instructed brain state(s) v. Rest, visual "distractor" cues (**Neutral, Cocaine; Aversive**) were superimposed on the ongoing cognitive control tasks. The "distractor" pictures occurred unpredictably in the periphery of the screen, and occurred during both the active and Rest phases of the tasks. The cue distraction spanned 36 sec (3 successive active v. rest cycles), and was counterbalanced for cue type across scans. The entire real-time fMRI session consisted of 4 scans; each scan featured 3, 128-sec epochs – with one period of distraction during each epoch (12 distraction periods overall; 4 of each cue type). **Analysis:** The analysis determined 1) whether the subjects were able to follow the demands of the task (indexed by *classification accuracy*), 2) whether appearance of the various distractor cues was associated with a "loss of control" (*loss* of classification accuracy) by frontal and comparison brain regions, and 3) whether the (Neutral, Cocaine and Aversive) distractor cues had a differential effect on limbic motivational circuitry, and on the two populations (cocaine patients and controls).
Results: 1) Both healthy controls and cocaine patients were able perform the basic cognitive control task (active v. Rest; all $t > 3$; $P < 0.0001$), though classifier accuracies were generally higher in the healthy controls. Cognitive control in the cocaine patients tended to fall off across the scan; reports of fatigue and boredom were more common in the patient population. 2) The distractor cues clearly impacted cognitive control, with evocative cues (especially aversive cues) producing more disruption in brain performance than the neutral cues, for both groups. The disruptive effects of cues were reflected across many brain regions, with frontal regions showing particular vulnerability in cocaine patients. 3) As hypothesized, the impact of distractor cues on limbic motivational circuitry (all $t > 2 < 5$) depended on the population: Aversive distractors had greater effects in controls, while the cocaine distractors had greater (limbic, extra-limbic, and visual circuitry) effects in the cocaine patients. As expected, Neutral distractors did not activate motivational circuitry – for either patients or controls.
Conclusions: These findings provide early encouragement that real-time fMRI paradigms can be used to model disruption of cognitive control by drug cues, and/or by other comparison cues. As hypothesized, the disruptive effects of evocative drug cues depended on drug use history: cocaine patients were more vulnerable to disruption by cocaine cues, relative to other cue types, and relative to the control population. As predicted, the evocative (but not the neutral) cues activated limbic motivational circuitry – offering a window onto the brain processes that can undermine cognitive control in patients and non-patients alike. Understanding the way in which the brain "loses control" is fundamental to developing (behavioral or medication) interventions that can improve control, and thus improve clinical outcome in addictions, and in other disorders characterized by compromised cognitive control. The current results form a critical foundation for the next stage of the research: testing whether real-time fMRI feedback can help individuals maintain cognitive control despite limbic disruption. The next stage of the work will also necessarily include elements (small incentives and game-like features) to enhance cocaine patients' engagement in the tasks, as engagement is a *sine qua non* for testing the potential benefit of real-time fMRI feedback.
Keywords: real-time fMRI, feedback training, cue reactivity, cognitive control
Disclosure: A. Childress, Nothing to Disclose; J. Magland, Nothing to Disclose; O. Bartra, Nothing to Disclose; J. Lupardus, Nothing to Disclose; R. Fabianski, Nothing to Disclose; S. Lam, Nothing to Disclose; K. Young, Nothing to Disclose; J. Suh, Nothing to Disclose; T. Franklin, Nothing to Disclose; D. Langleben, Nothing to Disclose; C. O'Brien, **Part 1:** Alkermes consulting, less than 10K, no interest in the company.

T182. Anomalous Insula-amygdala Functional Connectivity in Borderline Personality Disorder Patients is Associated with Impaired Psychological Habituation to Negative Stimuli

Harold W. Koenigsberg*, Bryan Denny, Jin Fan, Xun Liu,
Liza Rimsky, Hannah Pakray, Antonia S. New, Larry J. Siever

Mount Sinai School of Medicine, New York, New York

Background: Borderline personality disorder (BPD), a disorder characterized by emotional instability, interpersonal volatility, and a suicide rate of 10%, occurs in 2 to 5.9% of the population. Affective instability, a core feature of BPD, is strongly associated with the emotional and interpersonal symptoms of the disorder and with its suicidality, yet the neural dysregulations underlying borderline affective instability have not been clearly identified. One highly adaptive psychological mechanism that healthy individuals use for regulating negative affect is habituation. We hypothesized that BPD patients would show diminished behavioral habituation to repeated exposure to negative cues compared to healthy volunteers, and that this would be associated with anomalous neural processing of novel vs. repeated negative stimuli in regions critically associated with affective appraisal, including the amygdala and insula.
Methods: Nineteen BPD patients, 25 healthy volunteers (HC) and a psychopathological control group of 23 avoidant personality disorder patients (AvPD) were shown emotionally negative and neutral pictures depicting interpersonal interactions while fMRI

scans were obtained. Two thirds of the pictures were repeated approximately 5 minutes after initial presentation. Immediately after viewing each picture, subjects rated how positive or negative that picture made them feel. Group comparisons of the novel vs. repeat image contrasts were carried out using SPM8 and NeuroElf software. Changes in functional connectivity to a left insula seed region, when viewing novel vs. repeat pictures were examined for each group using a psychophysiological interaction analysis implemented in NeuroElf. The left insula seed region was selected as the conjunction across groups of a region that showed a significant correlation with trial-by-trial affect ratings for negative novel and repeat pictures. Finally, the association between changes in insula-amygdala connectivity and changes in summary affect rating was examined for each group.

Results: Consistent withpsychological habituation, HC subjects rated repeat negative pictures significantly less negative than novel negative pictures ($p = 0.01$), but BPD and AvPD subjects did not. BPD subjects showed larger decreases in activation when viewing repeat vs, novel pictures than HCs in left superior, left middle and right transverse temporal gyri and the dorsal anterior cingulate cortex. BPD subjects differed from AvPD subjects in showing greater sensitization (NegNovel < NegRepeat) in the right amygdala. HC subjects demonstrated increased connectivity between the left insula and amygdala when viewing repeat vs. novel pictures and, consistent with the finding of behavioral habituation, increased left insula-amygdala connectivity was associated with decreased negative affect when viewing repeat vs. novel pictures ($r = 0.490$, $p = 0.015$). BPD patients showed significantly less left insula-amygdala connectivity than HC's when viewing repeat vs. novel pictures, but increased connectivity was also associated with decreased negative affect in BPDs ($r = 0.525$, $p = 0.240$). AvPD patients also showed less of a change in insula-amygdala connectivity than HCs, but in contrast to both HCs and BPD patients, they showed a negative correlation between change in insula-amygdala connectivity and change in negative affect ($r = -0.516$, $p = 0.014$).

Conclusions: This study highlights the role of insula-amygdala connectivity in the regulation of negative affect and provides evidence that anomalies in this connectivity may be associated with impaired behavioral habituation in borderline patients. It also identifies differences in neural processes between BPD and AvPD patients when viewing repeat vs. novel emotional stimuli. BPD and AvPD patients do not psychologically habituate to repeated presentations of negative social pictures as HC's do. They also do not show the increase in functional connectivity between the left insula and amygdala when viewing repeated vs. novel pictures that HC subjects show. Since increased insula-amygdala connectivity is associated with decreases in negative emotional reactions to pictures as demonstrated in both BPD and HC subjects, an inability to adequately enhance insula-amygdala connectivity in BPD patients in response to repeated exposure to negative stimuli may contribute to the affective instability seen in BPD. In contrast to BPD's, AvPD subjects, who also do not enhance insula-amygdala connectivity, show the opposite relationship between change in insula-amygdala connectivity and change in affective response, i.e. they show a negative correlation between insula-amygdala connectivity and reduced affective negativity to repeat vs. novel pictures. These differences in functional connectivity among regions known to be critically important in affective appraisal may serve to further understanding of altered neural networks present in BPD and AvPD.

Keywords: insula, amygdala, connectivity, borderline personality disorder, avoidant personality disorder

Disclosure: H. Koenigsberg, Nothing to Disclose; B. Denny, Nothing to Disclose; J. Fan, Nothing to Disclose; X. Liu, Nothing to Disclose; L. Rimsky, Nothing to Disclose; H. Pakray, Nothing to Disclose; A. New, Nothing to Disclose; L. Siever, Nothing to Disclose.

T183. Effects of GABAergic Manipulation of Resting State Brain Networks in Psychotic and Healthy Subjects: A Connectomic Pattern Classification Analysis

Chandra Sripada, Robert C. Welsh, Daniel Kessler, K. Luan Phan, Stephan F. Taylor*

University of Michigan, Ann Arbor, Michigan

Background: Low frequency fluctuations in the blood oxygenation level dependent (BOLD) signal have identified cerebral networks with functional significance, providing clues to the large-scale organization of the brain and interregional connectivity. Most commonly studied during resting states independent of task (hence, 'intrinsic connectivity networks' or ICN's), differences in connectivity have been described in a number of psychiatric disorders, including schizophrenia. Relatively little is known about how various neurotransmitter systems interact with ICN's and how psychotropic drugs might modulate these networks. For instance, GABAergic interneurons are widely distributed throughout the brain. Post-mortem, physiologic and neuroimaging data implicate GABAergic dysfunction in schizophrenia, and pharmacologic manipulation of the GABAergic system ameliorates symptoms of psychosis. Thus, we undertook a study to examine the effects of the benzodiazepine, which potentiates GABA function, in psychotic and healthy individuals. Given the widespread distribution of GABAergic neurons, we employed a novel analytic machine-learning method to maximize the ability to evaluate drug-induced changes to ICN's, as well as group differences, across all networks of the brain.

Methods: Fourteen medicated schizophrenia/schizoaffective subjects (9M, age = 43), and 13 healthy controls (HC; 8M, age = 41.5) underwent resting state T2* BOLD imaging in a single-blinded, cross-over study using intravenous lorazepam (LRZ; 10 mcg/kg) and saline (separated by ~1-3 weeks). Our connectomic pattern classification analysis involved three major steps: *1) Connectome generation*: After standard preprocessing (slice-time correction, realignment, normalization, smoothing), connectomes were generated for each subject and session separately. A grid-based approach was utilized: 1080 4.35 mm radius spherical regions of interest (ROI) were placed at 12 mm intervals across the brain. The spatially–averaged BOLD time series was extracted from each ROI, and Pearson's correlations were calculated pairwise between each time series. Additional regressors controlled for motion and signal derived from white matter and cerebrospinal fluid. *2) Pattern classification*: A novel 'paired Support Vector Machine (SVM)' framework was implemented in order to account for the within-subject structure of the data (i.e., multiple scanning sessions from the same subject). SVM classifiers were trained separately to distinguish LRZ versus PBO separately in participants with schizophrenia and healthy participants. Univariate feature pruning was utilized and performance was assessed with {25, 50, 100, 500, 1000, 5000} retained features. Leave one out cross-validation was used to assess classifier performance, with feature pruning nested within the folds of the cross-validation to obviate bias. *3) Visualization*: For each trained classifier, we identified the set of edges that contributed to classification across every fold of the leave one out cross-validation ('the consensus discriminative connectome'). The network affiliation of the nodes associated with these edges was established according to the ICN parcellation scheme of Yeo and colleagues (2011).

Results: *Participants with schizophrenia*: Accurate classification of LRZ versus PBO was achieved at 50 features (12/14, binomial test $p = 0.01$) as well as 500 features (11/14, binomial test $p = 0.06$). The larger feature set was chosen for further analysis to provide a more comprehensive perspective on LRZ effects. The consensus discriminative connectome consisted of 256 edges. Four networks were overrepresented in the consensus connectome, accounting for 158 of these edges: somatomotor network (n = 77), default network (42 edges), ventral attention network (40 edges), and cerebellum (33 edges). Edges that involved the ventral attention network were mostly positive under PBO, and LRZ decreased connectivity in 25 out of 33 of these edges. *Participants with healthy controls*: Peak classification accuracy was achieved at 5000 features

(9/13), which was not statistically different from chance (binomial test $p = 0.27$). *Group differences*: Given accurate classification of LRZ versus PBO in schizophrenia, we next examined the discriminative connectome derived from schizophrenia participants in both schizophrenia as well as healthy participants, in order to better understand how LRZ differentially impacts connectivity in these two groups. There was general muting of connectivity changes induced by LRZ in the HC group compared to the schizophrenia group in the four major networks represented in the discriminative connectome. For example, mean connectivity change due to LRZ in the 77 edges involving the somatomotor network was -0.07 in participants with schizophrenia, but 0.01 in healthy participants, a highly statistically significant difference ($p < 0.001$).

Conclusions: We found that in participants with schizophrenia, acute administration of intravenous LRZ produced a reliable multivariate neural signature that enabled highly accurate classification of drug versus PBO. In particular, LRZ produced altered connectivity in somatomotor network, default network, ventral attention network, and cerebellum, consistent with the widespread distribution of GABAergic interneurons. In healthy individuals, LRZ did not generate a reliable connectomic signature, providing initial suggestive evidence that differences between the two groups in acute brain response to LRZ are present, and are represented in the resting state connectome. This study demonstrates the feasibility and utility of connectomic imaging coupled with multivariate pattern classification for characterizing the effects of psychotropic drug administration on distributed brain networks in clinical populations.

Keywords: resting state, connectomics, schizophrenia, lorazepam, pattern classification

Disclosure: C. Sripada, Nothing to Disclose; R. Welsh, Nothing to Disclose; D. Kessler, Nothing to Disclose; K. Phan, Nothing to Disclose; S. Taylor, Nothing to Disclose.

T184. Pretreatment Orbitofrontal Thickness as a Measure to Classify Patients with Obsessive-compulsive Disorder in Responders and Non-responders

Marcelo Q. Hoexter*, Antonio C Lopes, Roseli G. Shavitt, Marcelo Batistuzzo, Darin D Dougherty, Fabio L S Duran, Juliana Belo. Diniz, Geraldo F Busatto, Euripedes C Miguel, Rodrigo A Bressan, João R Sato

University of Sao Paulo Medical School, São Paulo, Brazil

Background: Rates of response to gold standard treatments (serotonin reuptake inhibitors and/or cognitive-behavioral therapy) vary immensely among individuals with obsessive-compulsive disorder (OCD). Until now, there is not a reliable neurobiological measure to indicate whether a patient will be a treatment responder or a non-responder. Given the central role of the orbitofrontal cortex in the pathophysiology of OCD, we hypothesize that this region may potentially contain discriminative information to predict treatment response. The aim of this study was to determine whether orbitofrontal cortex thickness has clinical value in classifying OCD patients in treatment responders or non-responders.

Methods: Twenty-nine treatment-naïve adult patients with OCD underwent a clinical trial with standard treatments for OCD (fluoxetine or cognitive-behavioral therapy) and were classified as responders and as non-responders after 12 weeks of follow-up. Treatment response was defined as a minimum reduction of 35% on the Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) and a 'much-improved' or 'very-much-improved' on the Clinical Global Impression scale (CGI) for OCD. Logistic regression analysis was used for classifying treatment response, i. e., pretreatment orbitofrontal cortex thickness obtained from structural magnetic resonance imaging (MRI) was used as a predictor continuous independent variable whereas treatment response (responders and non-responders) was used as a categorical dependent variable (outcome).

Results: After 12 weeks of treatment, 13 patients with OCD were considered responders whereas 16 were non-responders. Pretreatment left medial orbitofrontal cortex was thicker in patients who responded to standardized treatments for OCD compared with non-responders ($p = 0.027$). Pretreatment thickness of the medial orbitofrontal cortex classified patients as responders and as non-responders with 79.3% accuracy (81% sensitivity, 77% specificity) and 0.88 Area Under the Receiver Operating Curve (AUC). From 13 patients who fulfilled criteria for treatment response, 3 were misclassified as non-responders (23%). From 16 patients who were considered treatment non-responders, 3 were misclassified as responders (19%).

Conclusions: Our findings suggest that pretreatment orbitofrontal cortex thickness could be a predictor of response to standard treatments for OCD. Given the small sample size of the present study, future neuroimaging longitudinal treatment studies with larger samples of OCD patients should be performed to confirm these results.

Keywords: Obsessive-compulsive disorder, orbitofrontal cortex, cortical thickness, prediction, treatment response

Disclosure: M. Hoexter, Nothing to Disclose; A. Lopes, Nothing to Disclose; R. Shavitt, Nothing to Disclose; M. Batistuzzo, Nothing to Disclose; D. Dougherty, Nothing to Disclose; F. Duran, Nothing to Disclose; J. Diniz, Nothing to Disclose; G. Busatto, Nothing to Disclose; E. Miguel, Nothing to Disclose; R. Bressan, Nothing to Disclose; J. Sato, Nothing to Disclose.

T185. Amygdala, Prefrontal Cortex, and Cingulate Relationships in Combat Veterans with Traumatic Brain Injury and Post-traumatic Stress Disorder

Monte S. Buchsbaum*, Alan Simmons, Alex DeCastro, Scott Matthews

University of California, San Diego, California

Background: Although the mechanism is incompletely understood, persistent symptoms after mild traumatic brain injury occur in a significant fraction of individuals. Related evidence indicates that individuals who experience mild traumatic brain injury (TBI) are at increased risk for major psychiatric disorders such as posttraumatic stress disorder (PTSD). Our fMRI research suggests that amygdala hyperactivity viewing fearful faces may be associated with PTSD in combat veterans and that amygdala to subgenual cingulate may be strengthened in these patients. However PTSD in injured individuals might arise from different patterns of connectivity disruptions.

Methods: We examined this in three groups of patients: combat veterans with a history of mild traumatic brain injury, combat veterans with both mild traumatic brain injury and post-traumatic stress disorder, and combat veterans without either condition. 18-F-flurodeoxyglucose positron emission tomography scans were obtained while subjects carried out a verbal learning test to standardize conditions.

Results: We first examined the sizes of contiguous clusters of voxels that were 2 SD below the mean of the healthy combat veterans and found that the clusters were significantly larger for both TBI and for PTSD and TBI groups, consistent with both suffering a traumatic brain injury. Patients with PTSD and TBI had lower amygdala FDG uptake than combat controls. Combat veterans with traumatic brain injury tended to have lower dorsolateral and higher medial prefrontal activity while combat veterans with traumatic brain injury and PTSD had higher dorsolateral prefrontal activity (group by brain region (sup. and inf. Amygdala, dorsolateral BA 44-45, and medial BA 25 and 32, $F = 3.93$, $df = 4,90$, $p = 0.0054$). Thus, TBI patients in general tended to raise prefrontal activity while carrying out a cognitive task with PTSD + TBI patients raising dorsolateral activity above combat controls and TBI alone patients primarily raising medial prefrontal regions above combat controls.

Conclusions: Our results indicate that patients with both TBI and PTSD may not fully resemble patients with PTSD alone in amygdala activation and that different mechanisms may be involved in these PTSD patients. Patients with TBI alone may shift functional activity to medial frontal cortex from possibly damaged lateral areas. Lastly, the choice of a cognitive task vs emotional task may greatly affect the relative balance of activity between the frontal lobe and the amygdala.

Keywords: Fluorodeoxyglucose, positron emission tomography, prefrontal cortex, basal amygdala, combat veterans
Disclosure: M. Buchsbaum, **Part 2:** Elsevier Publishing, **Part 4:** Profil Research, San Diego, Novartis, St. Jude's Neuromodulation: No relationship between these projects and the current work; A. Simmons, Nothing to Disclose; A. DeCastro, Nothing to Disclose; S. Matthews, Nothing to Disclose.

T186. White Matter Integrity in the Anorexic Brain

Laurie M. McCormick*, Brendan Hodis, Michael Brumm, Joseph Caballero

University of Iowa Carver College of Medicine, Iowa City, Iowa

Background: Anorexia nervosa (AN) has the highest mortality rate of any psychiatric illness. It occurs primarily in females, less than half of whom ever fully recover. The lifetime prevalence of AN in the US is 1%, the same as that of schizophrenia. Bothconditions are associated with high levels of alexithymia and social cognitionproblems. Previous studies have shown that there is global atrophy in both grayand white matter throughout the cortex during the starvation phase of AN, butthat these regions tend to revert back to normal with weight restoration. Fewstudies have examined potential cortical white matter tract integrity changesdue to starvation in AN. The consistent observation of weight related whitematter changes in AN, combined with a paucity of studies examining focal whitematter integrity, prompted an investigation of regional diffusion within whitematter of the starved AN brain.
Methods: Structural magnetic resonance imaging (MRI), diffusion MRI, and clinical data were collectedfrom a group of females during hospitalization for the treatment of acute AN($n = 18$), after weight restoration during hospitalization ($n = 13$), as well as froma group of age and gender-matched healthy controls ($n = 16$). Using Free Surfer, a set of tools for automated reconstruction of the brain's cortical surface, cortical parcellations and parcellations of associated subcortical white matter were generated in T1-space. On locally developed software, tensors were calculatedfrom the diffusion-weighted scans on a voxel-wise basis and fractionalanisotropy (FA) was calculated at each voxel to yield full FA volumes. FAimages were then co-registered to T1-weighted structural images. Using subcorticalwhite matter masks generated by FreeSurfer, we calculated local mean FA in eachsegmented white matter parcellation for all subjects. Each region was comparedbetween groups using a two-sample unpaired *t*-test assuming unequal variances. The Toronto Alexithymia Scale (TAS) and its 3 factors (difficulty identifyingfeelings, difficulty describing feelings, and externally oriented thinking) wereapplied to AN and control groups in order to quantify personality changesassociated with AN. Correlations between TAS factors and regional mean FAvalues were calculated.
Results: The AN group had significantly lower body mass index (BMI) during starvation (16 vs. 25) and higher levels of alexithymia (58 vs 36) than the control group. WhileBMI was significantly restored in the AN group ($BMI = 20$), there was nosignificant change in TAS after weight restoration. There were no significantdifferences in mean white-matter FA using whole brain ($p = 0.090$), left hemisphere ($p = 0.105$), or right hemisphere ($p = 0.0877$) masks betweenthe AN group during starvation and controls. However, there was a significant reductionin white matter FA underlying the right inferior frontal gyrus in ($p = 0.003$) in the AN group during starvation. Subdividing this region into its major anatomical subdivisions, we were able tofurther describe the reduction in white matter underlying the pars opercularis ($p = 0.003$), the pars triangularis ($p = 0.033$) and the pars orbitalis ($p < 0.000$). There was a strong negativecorrelation between TAS factor II (Difficulty Describing Feelings) and rightpars orbitalis mean FA ($r = -0.49$; $p = 0.004$). While both the parsopercularis and pars triangularis mean FA values increased with weightrestoration in the AN group, there was no significant change in FA values forthe pars orbitalis with weight restoration.
Conclusions: This is the first study to show that white matter FA underlying the right inferiorfrontal gyrus is reduced during starvation in AN. It is also the first to showthat white matter FA specifically in the right pars orbitalis is highlyassociated with difficulty describing feelings and that both don't changesignificantly with weight restoration, suggesting that this is possibly a vulnerabilityfactor for developing AN. This report represents a cross-section from an ongoing study, and we expect thatadditional trends will reach significance as further data collection improvesour statistical power.
Keywords: anorexia nervosa, fractional anisotropy, right inferior frontal gyrus, pars orbitalis
Disclosure: L. McCormick, Nothing to Disclose; B. Hodis, Nothing to Disclose; M. Brumm, Nothing to Disclose; J. Caballero, Nothing to Disclose.

T187. Association of Glutamate and N-acetylaspartate in Schizophrenia before and after Treatment with Risperidone: a Proton Magnetic Resonance Spectroscopy Study

Adrienne C. Lahti*, Meredith A. Reid, Nina V. Kraguljac, David M. White, Jan den Hollander

University of Alabama, Birmingham, Alabama

Background: Postmortem evidence in schizophrenia points to abnormal function of the glutamate–glutamine cycle as well as mitochondria. Since glutamate and *N*-acetylaspartate (NAA) are linked through the tricarboxylic acid and glutamate–glutamine cycles, it suggests disruption of the homeostasis of these metabolites. In a study comparing 48 stable, medicated patients with schizophrenia to 46 healthy controls, we used magnetic resonance spectroscopy (MRS) to investigate the relationship between glutamate + glutamine (Glx) and NAA in the anterior cingulate cortex (ACC) and hippocampus (HIP), two regions frequently associated with the illness. In controls, Glx and NAA were positively correlated in both regions. In patients, we found a de-coupling of Glx and NAA in the HIP but not the ACC (Kraguljac et al, In Press). Since these regions have been linked to psychosis and treatment response, we sought to evaluate this relationship before and after treatment with risperidone. We tested the hypothesis that Glx and NAA would be de-coupled in the ACC when the patients were unmedicated and that this would be reversed by the antipsychotic medication (APD) risperidone.
Methods: We examined the relationship between Glx and NAA in 20 patients with schizophrenia, each scanned at 3 time points: while they were off medication (at least 10 days), after 1 week of treatment, and after 6 weeks of treatment with risperidone. Using a 3T MR scanner, we obtained MRS spectra from the HIP and dorsal ACC using the point resolved spectroscopy sequence (PRESS; TR/TE = 2000/80 ms to optimize the glutamate signal). Glx and NAA were quantified with respect to creatine (Cr) using jMRUI. Pearson correlation was used to investigate the association between Glx/Cr and NAA/Cr. The Brief Psychiatric Rating Scale (BPRS) was used to assess symptom change.
Results: There was no difference in Glx/Cr or NAA/Cr levels over time for both regions. In the ACC, the correlation between Glx/Cr and NAA/Cr was not significant when patients were off medication ($r(18) = .28$, $p = .24$); however, these metabolites were significantly positively correlated after one week($r(18) = .69$, $p = .001$) and 6 weeks ($r(18) = .55$, $p = .01$) of treatment. In the hippocampus, the correlations between Glx/Cr and NAA/Cr were non-significant at all 3 time points (all $p > .50$). In addition, there was a positive correlation between the off-medication Glx/Cr level in the ACC and the percent change in BPRS total score after 6 weeks of treatment ($r(18) = .46$, $p = .04$).
Conclusions: These findings replicate and extend our previous results suggesting that in schizophrenia there is disruption of the homeostasis of glutamate and NAA in the hippocampus. This association was not affected by 6 weeks of treatment with risperidone. These results suggest that de-coupling of glutamate and NAA in the hippocampus may represent a trait marker of schizophrenia. Also replicating our prior results, we found coupling of NAA and glutamate in the ACC when the patients were medicated; however, as hypothesized, the coupling was not observed when the patients were unmedicated. Finally, we found that

higher ACC glutamate levels in unmedicated patients were correlated with good response to risperidone, suggesting that ACC glutamate could potentially be used as a biomarker of treatment response. Nina K Kraguljac, Meredith A Reid, David M White, Jan A den Hollander, Adrienne C Lahti. Regional Decoupling of N-Acetyl-Aspartate and Glutamate in Schizophrenia. In Press. Neuropsychopharmacology. This work was funded through the NIMH grant R01 MH081014 (ACL).

Keywords: schizophrenia, glutamate, n-acetylaspartate, risperidone, proton magnetic resonance spectroscopy

Disclosure: A. Lahti, Nothing to Disclose; M. Reid, Nothing to Disclose; N. Kraguljac, Nothing to Disclose; D. White, Nothing to Disclose; J. den Hollander, Nothing to Disclose.

T188. Multimodal Neuroimaging Correlates of Repetitive Mild Traumatic Brain Injury in Iraq and Afghanistan War Veterans

Eric C. Petrie*, Donna J. Cross, Vasily Yarnykh, Todd Richards, Nathalie Martin, Satoshi Minoshima, Murray A. Raskind, Elaine R. Peskind

VA Puget Sound Health Care System, Seattle, Washington

Background: Whether chronic postconcussive symptoms (PCS) reported by Iraq and Afghanistan Veterans with repetitive mild traumatic brain injury (Blast-mTBI Veterans) are associated with structural and/or functional brain abnormalities vs. comorbid psychiatric conditions, such as posttraumatic stress disorder (PTSD) and depression, remains unclear. Recent reports of pathologically hyperphosphorylated tau protein observed postmortem in the brains of a small number of Iraq and Afghanistan Veterans have raised concerns that this cohort of Veterans may be at risk for chronic traumatic encephalopathy. As a result, efforts to develop non-invasive methods to detect putative structural and/or functional brain abnormalities in Iraq and Afghanistan Veterans with repetitive mTBI have assumed greater urgency. We carried out multimodal structural and functional brain imaging studies and extended clinical assessments in a cohort of Iraq and Afghanistan Veterans with and without repetitive mTBI.

Methods: Blast-mTBI Veterans (N = 34, all male, 31.6 ± 9.2 [mean ± standard deviation] years of age) had sustained one or more explosive blast related mTBIs (American Congress of Rehabilitation Medicine criteria) during war zone deployment. Nonblast Veterans (N = 16, 15 M, 1F, 32.8 ± 7.3 years of age) were deployed to Iraq or Afghanistan but had history of mTBI, except for one with a single impact head injury at age 16 in which he was briefly dazed and confused. Brain FDG-PET images were acquired on a GE Advance scanner. Voxel intensity was normalized to global brain activity. Brain FA and source images for MPF mapping were acquired on a 3.0 T Philips Achieva scanner. FA images were acquired with 32 gradient directions and b-factors = 0 and 1,000s/mm^2. Brain MPF mapping utilized 3D-spoiled gradient-echo sequences with and without a 4 kH off-resonance saturation pulse; variable flip angle T1 mapping; and actual flip angle B1 mapping. Whole-brain voxelwise comparisons of CMRglu; FA; and MPF in Nonblast vs. Blast-mTBI Veterans were performed with NEUROSTAT software (UW, Seattle, WA) in Talairach atlas space. A random fields approach with significance set at a conservative value of Z = 4.0 was used to control the Type-I error rate at approximately P = 0.05 for multiple comparisons. Group-wise comparisons of CMRglu, FA, and MPF Volumes-of-Interest (VOI) and non-imaging data were performed using one-tailed *t*-tests (P = 0.05), based on *a priori* hypotheses of more abnormal imaging metrics and behavioral and neurologic symptoms in Blast-mTBI vs. Nonblast Veterans.

Results: Blast-mTBI Veterans experienced 13.2 ± 16.8 blast-mTBI events while deployed to Iraq or Afghanistan. They experienced a total of 19.6 ± 26.0 blast mTBI events during their entire period of military service. Nine percent had experienced a single blast-mTBI during military service; 29.4% had 2-5; 20.6% had 6-10; 6% had 11-15; 14.7% had 16-20; 9% had 21-50; and 11.8% had 51-100. Mean time between last blast-mTBI and study enrollment was 3.8 ± 1.5 years. Compared to Nonblast Veterans, Blast-mTBI Veterans exhibited reduced FA in the corpus callosum (20.7% to 28.1%, p's < 0.001); reduced MPF in numerous subgyral, cortical-subcortical, and longitudinal white matter (WM) tracts (Zs > 4.0); reduced CMRglu in parietal, somatosensory, and visual cortices (1.6% to 3.4%, p's < 0.050); and higher scores on measures of PCS, PTSD, combat exposure, depression, sleep disturbance, and alcohol use. Blast-mTBI Veterans with vs. without PTSD did not differ with respect to measures of FA, MPF, or CMRglu.

Conclusions: Iraq and Afghanistan Veterans with repetitive mTBI exhibit abnormalities of brain WM structural integrity and macromolecular organization and brain glucose metabolism, consistent with recent neuropathologic evidence of chronic brain injury in this cohort of Veterans. These abnormalities are not explained by the presence or absence of PTSD.

Keywords: PTSD, TBI, concussion, imaging, Veterans

Disclosure: E. Petrie, Nothing to Disclose; D. Cross, Nothing to Disclose; V. Yarnykh, Nothing to Disclose; T. Richards, Nothing to Disclose; N. Martin, Nothing to Disclose; S. Minoshima, Nothing to Disclose; M. Raskind, Nothing to Disclose; E. Peskind, Nothing to Disclose.

T189. Early Life Stress and Functional Connectivity within Major Depression

Merida Grant*, Jennifer Hadley, David M. White, Richard C. Shelton

UAB, Birmingham, Alabama

Background: Differential pathophysiology within major depression (MDD) based on early life stress history is associated with two distinct phenotypes; (1) a hyper-responsive subtype characterized by exaggerated amygdala reactivity and decreased anterior cingulate volume (BA 32/24) among trauma-exposed MDD and (2) a hypo-responsive subtype associated with attenuated limbic reactivity and unaffected cingulate volume among never trauma-exposed MDD (Grant et al 2011; Treadway et al 2009). Translational models of stress (Christianson et al 2009) as well as imaging findings in non-clinical human studies (Wood et al 2012) have demonstrated key roles for medial and lateral prefrontal cortex (e.g., anterior cingulate and dorsal lateral PFC) in modulation of limbic response to stress. The current study investigated whether differential amygdala reactivity within MDD based on early life stress history was associated with failure of inhibition from medial or lateral PFC.

Methods: Twenty unmedicated patients with MDD and 19 healthy controls (HC), matched for age, education and IQ, were administered the Childhood Trauma Questionnaire (CTQ-SF) and scanned using functional magnetic resonance imaging (fMRI) while passively viewing sad and neutral faces. After standard preprocessing, ROI-based functional connectivity maps were created using the Pearson's correlation coefficient between the seed region's fMRI time series and whole brain. ROI functional connectivity maps were then compared using a factorial random effects model to assess differences between participant groups. Individual differences in the relationship between CTQ scores on the physical (PA) and sexual abuse (SA) subscales and seed-based connectivity were then examined for each group in addition to analysis of variance. All comparisons were reported using a FDR corrected p-value of 0.01.

Results: Significant correlations were observed among both MDD and HC employing either left amygdala or BA 46/9 (dorsal lateral PFC) as seed regions. Within MDD, left BA 46/9 demonstrated an inverse relationship with BA 32, while a positive correlation between BA 46/9 and BA 32 was observed within HC. Elevated CTQ-PA scores were associated with increased connectivity between left amygdala and BA 25 within MDD. In contrast, CTQ-PA was associated with an inverse correlation between left amygdala activity and BA 25 and thalamus in HC. No significant relationships were observed for CTQ-SA following FDR correction.

Conclusions: Findings from the current investigation were consistent with individual and between group differences in connectivity in response to aversive stimuli among MDD and HC based on early life

stress history and subsequent influence of lateral and medial PFC modulation of amygdala.
Keywords: Imaging, MDD, early life stress, amygdala, cingulate
Disclosure: M. Grant, Nothing to Disclose; J. Hadley, Nothing to Disclose; D. White, Nothing to Disclose; R. Shelton, Nothing to Disclose.

T190. Dopaminergic Activity and Altered Reward Modulation in Anorexia Nervosa

Ursula F. Bailer*, Julie C. Price, Carolyn C. Meltzer, Angela Wagner, Chester A. Mathis, Walter H. Kaye

University of California San Diego, La Jolla, California

Background: Several lines of evidence suggest that individuals with anorexia nervosa (AN) have altered striatal dopamine (DA) function. Using the radioligand [11C]raclopride and positron emission tomography (PET), we have recently found that individuals recovered (REC) from AN (REC AN) have increased binding of DA D2/D3 receptors at baseline in the anterior ventral striatum (AVS) relative to control women (CW) (Frank, 2005; Bailer, In Press). Moreover, [^{11}C]raclopride $BP_{Non-displacebale(ND)}$ in the dorsal caudate was associated with harm avoidance, a measure of anxiety, in REC AN (Frank, 2005; Bailer, In Press). DA disturbances in AN may contribute to an altered modulation of appetitive behaviors. Animal studies indicate that DA in the striatum plays a key role in the optimal response to reward stimuli. To further understand striatal DA pathways and the relationship to reward, our group performed a fMRI study using a monetary choice task known to activate the striatum. REC AN (Wagner, 2007) failed to have a differential AVS response to positive and negative monetary feedback compared to CW. However, REC AN showed greater hemodynamic activation in the caudate than CW. Only REC AN showed a significant positive relationship between trait anxiety and the percentage change in hemodynamic signal in the caudate during either wins ($r = .68$, $p = .01$) or losses ($r = .74$, $p = .004$). Do such correlations imply that PET [^{11}C]raclopride BP_{ND} might be related to the BOLD response to monetary choice in the dorsal caudate of REC AN?
Methods: We have done a post-hoc analysis of our PET and fMRI data and correlated baseline [^{11}C]raclopride BP_{ND} and BOLD signal in eleven REC AN (age 27 ± 7, BMI 20.5 ± 2.1) and 6 CW (age 30 ± 7, BMI 22.9 ± 2.6) who participated in both the fMRI study using the monetary choice task and the [^{11}C]raclopride PET study.
Results: REC AN showed a positive relationship between [^{11}C]raclopride BP_{ND} and the BOLD signal in the dorsal caudate in response to losses ($r = .71$, $p = .01$) or wins ($r = .64$, $p = .03$), but not for the AVS (losses $r = .29$, ns; wins $r = .19$, ns). Despite the small sample, there was a suggestion that CW had different relationships. That is, stronger finding between [^{11}C]raclopride BP_{ND} and the BOLD signal in the AVS in response to losses ($r = .85$, $p = .03$) or wins ($r = .63$, $p = .18$), but not for the dorsal caudate (losses $r = -.34$, ns; wins $r = .52$, ns).
Conclusions: These findings show that in REC AN, DA D2/D3 receptor binding in the dorsal caudate was positively associated with the BOLD response to both wins and losses in a monetary choice task, whereas no such associations were found in the AVS. In contrast, CW showed positive correlations for both wins and losses in the AVS, but not in the dorsal caudate. These data are consistent with other imaging data showing that measures of DA metabolism tend to be associated with AVS activation in CW, and dorsal caudate activation in AN. It is well known that AN have exaggerated inhibition and anxiety, and are insensitive to reward. It may be that AN have an imbalance between ventral limbic and dorsal executive processes. Perhaps ventral limbic-striatal circuitry may be inhibited by "hyperactive" inputs from dorsal executive processes (Kaye, in press), a theory supported by recent animal studies showing that dorsal caudate D2 receptor function plays a key role in risk avoidance and inhibition. Moreover, our recent study (Bailer 2011) supports the possibility that food-induced DA release in the dorsal caudate stimulates anxiety in AN. From a clinical perspective, it is very difficult to find "rewards" that AN individuals value more than food restriction, and AN individuals may in fact find that food refusal to be an effective means of diminishing anxiety. Thus, these insights may be of value in developing an effective treatment for this devastating disorder.
Keywords: anorexia nervosa, dopamine, reward, positron emission tomography, fMRI
Disclosure: U. Bailer, Nothing to Disclose; J. Price, Nothing to Disclose; C. Meltzer, Nothing to Disclose; A. Wagner, Nothing to Disclose; C. Mathis, **Part 1:** Dr. Mathis has received royalty payments for licensed technology from GE Healthcare and Neuroptix. Dr. Mathis also served as a consultant for Janssen/Elan, Wyeth/Pfizer, and Novartis, **Part 4:** research grant support from Neuroptix; W. Kaye, **Part 1:** Dr. Kaye has received salary support from the University of Pittsburgh and the University of California, San Diego; Research funding for an investigator initiated treatment study from Astra-Zeneca and consulting fees from Lundbeck and Merck. In addition, there are honoraria for presentations from academic institutions and meetings, and compensation for grant review activities from the National Institutes of Health.

T191. Imaging Emotion Circuits to Predict Treatment Outcomes in Major Depressive Disorder: The International Study to Predict Optimized Treatment in Depression

Leanne Williams*, Mayuresh Korgaonkar, Yun Ju Song, Sarah Eagles, Anthony Harris, Stephen Koslow, Stuart Grieve, Amit Etkin

University of Sydney Medical School and Westmead Millennium Institute, Stanford, California

Background: Major depressive disorder (MDD) is highly comorbid with anxiety, which is important in treatment prediction. MDD and anxiety also share dysfunction in cortico-limbic circuitry. The International Study to Predict Optimized Treatment in Depression (iSPOT-D) is a practical trial coupled with multiple measures of brain structure and function, designed to identify predictors and moderators of outcome for commonly used antidepressant medications. Here we used functional magnetic resonance imaging (fMRI) to focus on the anterior cingulate cortex (ACC)–amygdala circuits implicated in the emotional dysregulation features of MDD. We also considered the role of anxiety, given the heterogeneity of MDD, and the involvement of these same ACC circuits in anxiety disorders.
Methods: In iSPOT-D, we have completed assessments for the first planned testing phase: $n = 1008$ with MDD, and 336 matched healthy controls. The MDD participants were randomized to one of three treatment arms: escitalopram, sertraline and venlafaxine-XR ($n = 336$ in each). This sample represents the first planned half of the target total. Of these, approximately 10% ($n = 102$ MDD, $n = 34$ controls) were scanned using fMRI at the unmedicated baseline. Within the sample, 42% of MDD patients had a comorbid anxiety disorder. We probed emotional processing by presenting faces displaying one of multiple expressions (fear, sad, angry, disgust, happy, neutral) under one of two conditions: explicit conscious (unmasked) and implicit nonconscious (backward masking). We used multivariate techniques to compare MDD to controls at their unmedicated baseline, and regression analyses to test for prediction of treatment outcome by baseline activation. Outcome was assessed by symptoms of depression and anxiety, using both clinical ratings and self-report.
Results: MDD was characterized by a reduction in activation of the ACC compared to their healthy peers, at the unmedicated baseline. Moreover, the same region was implicated in predicting treatment outcome, specifically for patients with comorbid anxiety. ACC activation predicted post-treatment improvement in symptoms of depression and anxiety under both explicit and implicit processing of emotion conditions. This predictive relationship was characteristic of MDD patients with comorbid anxiety at the pre-treatment baseline.
Conclusions: Results from iSPOT-D imaging of emotion processing to date suggest that ACC circuits have a role in predicting which patients improve with treatment, overlapping with their role in the pathophysiology of the illness itself. Interactions between imaging predictors and

anxiety are consistent with the clinical relevance of considering anxiety in the management of MDD. A goal of iSPOT-D is translation. Our next steps are to examine ACC connectivity predictors, identify common and specific predictors across imaging modalities, how these imaging predictors relate to physiology and behavior, and to ultimately determine their cost-benefit and feasibility for the management of MDD in practice.
Keywords: Depression, Imaging biomarker, Emotion circuits, Anterior cingulate, Treatment prediction
Disclosure: L. Williams, **Part 2:** Brain Resource, consultant, **Part 4:** Brain Resource, funder of iSPOT-D; M. Korgaonkar, Nothing to Disclose; Y. Song, Nothing to Disclose; S. Eagles, Nothing to Disclose; A. Harris, **Part 4:** Brain Resource, funder of iSPOT-D (on which I am PI for Sydney site); S. Koslow, **Part 2:** Brain Resource, consultant, **Part 4:** Brain Resource, sponsor for iSPOT-D; S. Grieve, **Part 2:** Brain Resource, consultant; A. Etkin, Nothing to Disclose.

T192. Strength of Frontal-hippocampal Functional Coupling Predicts Hippocampal Responses during Fear Learning in Schizophrenia

Garth Coombs, Donald Goff, Mohammed R. Milad, Daphne J. Holt*

Harvard Medical School and Massachusetts General Hospital, Charlestown, Massachusetts

Background: Patients with schizophrenia show abnormalities in emotional learning. Some of these abnormalities have been linked to symptoms of the disorder, including negative symptoms and delusions. Moreover, neuroimaging studies have detected abnormalities in schizophrenia patients in the structure and function of brain areas mediating emotional learning, including regions of the medial temporal lobe (MTL; the amygdala and hippocampus) and medial prefrontal cortex (mPFC). In fact, patients with schizophrenia show abnormal MTL activity during the acquisition of conditioned fear responses. However, it is unclear whether this abnormality is related to an intrinsic abnormality of the MTL or to disruption of MTL inputs. Human and rodent studies have demonstrated that although fear learning and expression require the amygdala, distinct subregions of the mPFC are involved in the facilitation and inhibition of fear. For example, in the rodent, the prelimbic region of the mPFC facilitates MTL activity during fear learning. The dorsal anterior cingulate cortex (dACC) in the human brain is believed to represent the human homologue of the rodent prelimbic cortex, in part because its activity (measured by functional magnetic resonance imaging, fMRI) has been found to correlate with the magnitude of conditioned fear responses (measured by skin conductance responses), suggesting that the dACC, similar to the rodent prelimbic cortex, facilitates fear learning. Since the dACC and MTL are known to be reciprocally connected in primates, it has been proposed that projections from the dACC to the MTL facilitate MTL-mediated fear learning in humans. In light of the large body of evidence for structural and functional abnormalities of the dACC and MTL in schizophrenia, in the current investigation we sought to determine whether impaired MTL function during fear learning in schizophrenia is linked to an abnormal reduction in dACC-MTL functional connectivity.
Methods: Twenty patients who met DSM-IV criteria for schizophrenia and seventeen demographically-matched healthy subjects underwent Pavlovian fear conditioning while functional MRI data were simultaneously collected on a 3T Tim Trio Siemens scanner. During fear conditioning, an electric shock, delivered to the fingers, was paired with the presentation of two lights (the CS+), whereas a third light was never paired with a shock (the CS-). Also, one six-minute resting-state blood oxygenation level-dependent (BOLD) scan was collected during the same scan session. Amygdala and hippocampal activation during fear conditioning was measured using the FreeSurfer fMRI analysis stream (www.surfer.nmr.mgh.harvard.edu). A seed-based functional connectivity analysis was then conducted using 3 mm radius spherical seeds that were centered around the peak between-group differences found in the MTL in the analysis of the fear conditioning fMRI data.
Results: Controls showed greater activation than schizophrenic patients during fear conditioning in the left amygdala and bilateral hippocampus. The functional connectivity analyses revealed that the controls showed significant functional coupling between the right hippocampus and dACC, whereas the schizophrenic patients failed to show this coupling. Moreover, the magnitude of coupling between the right hippocampus and the dACC was positively correlated with the magnitude of the responses of the right hippocampus during fear conditioning in both the control ($p = .002$) and schizophrenia ($p = .001$) groups.
Conclusions: These findings suggest that impaired communication between the hippocampus and dACC may underlie deficient fear learning in schizophrenia. Future studies will investigate whether changes in fear learning over time in healthy subjects and schizophrenic patients are associated with changes in hippocampal-dACC connectivity and hippocampal function.
Keywords: fear, hippocampus, cingulate cortex, schizophrenia, connectivity
Disclosure: G. Coombs, Nothing to Disclose; D. Goff, **Part 1:** In the past 2 years, Dr. Goff has consulted to Roche, Eli Lilly, Takeda, BMS, Abbott, Genetech and Endo Pharmaceuticals and served on a DSMB for Otsuka. He has applied for patents regarding genetic predictors of response to glutamatergic agents and folate, **Part 4:** Dr. Goff received research funding from Pfizer, PamLab, Novartis and GSK; M. Milad, Nothing to Disclose; D. Holt, Nothing to Disclose.

T193. Functional Connectivity in Ventromedial Prefrontal Cortex is Altered in Depression: A Novel Biomarker Supported by Parallel Rodent and Human Neuroimaging Studies

Conor Liston*, Logan Grosenick, Karl Deisseroth, Wenbiao Gan, Marc Dubin

Stanford University, Stanford, California

Background: Clinical, translational, and basic neuroscience studies of mood disorders are hindered by our limited understanding of the underlying pathophysiology and in particular, by the lack of an objective and reliable biomarker for depression. Fixed tissue studies in animal models have demonstrated synapse loss in the hippocampus, medial prefrontal cortex (mPFC), and other limbic areas, raising the possibility that depression may arise in part from dysfunctional synaptic plasticity in limbic brain circuits. But synaptic remodeling cannot be studied directly in fixed tissue, and it remains unclear how these findings in rodents may relate to pathophysiology in patients.
Methods: To address these questions, we conducted parallel rodent and human neuroimaging studies. We used 2-photon *in-vivo* microendoscopy and optogenetic tools to study synaptic remodeling in the hippocampus (CA1, CA3) and mPFC in a chronic stress model of depression in mice. Repeated images of YFP-expressing pyramidal cells were acquired at 3- to 5-day intervals over 3-6 weeks, allowing us to quantify dendritic spine formation and elimination rates and to track the fate of newly formed spines over time. In a parallel series of human neuroimaging studies, we used resting state fMRI to identify changes in hippocampal and prefrontal functional connectivity in 1) chronically stressed but otherwise healthy human subjects; 2) currently depressed patients meeting DSM-IVR criteria for a major depressive episode; and 3) currently euthymic patients with a history of major depressive disorder. Stress- and depression-related abnormalities were identified based on normative connectivity maps generated from a pool of 250 age- and sex-matched healthy controls.
Results: Chronic stress increased both spine formation and elimination rates in CA1, CA3, and mPFC in a mouse model of depression. However, the long-term survival of newly formed spines was reduced, and elimination increased to a greater degree than formation. The net effect was a gradually accumulating loss of synapses—particularly synapses formed early in development-

—and associated changes in functional connectivity. In chronically stressed human subjects, widespread changes in functional connectivity were observed in both ventromedial PFC and hippocampus, but there was significant individual variability and the overall effect size was relatively modest. In contrast, currently depressed patients exhibited functional connectivity abnormalities that resembled in part the patterns observed in the chronically stressed group, but were more severe and highly consistent. Notable effects included reduced functional connectivity between subgenual cingulate cortex, the hippocampus, and brainstem areas encompassing the locus coeruleus and raphe nucleus, and increased connectivity between ventral PFC, subgenual cingulate, and ventral striatum. Some — but not all — of these abnormalities reversed in patients in full clinical remission. We used binomial logistic regression and multivariate pattern analysis to determine whether these connectivity effects could reliably distinguish individual depressed subjects from healthy controls, and achieved a 98.5% accuracy rate, including 100% accuracy for classification of depressed patients. Importantly, a separate index of connectivity measures could be used to identify currently euthymic MDD patients with 96% accuracy, again including 100% correct identification of patients. Finally, to assess these potential biomarkers for generalizability and specificity, we tested them in an independent cohort comprising patients with depression, patients with anxiety disorders, and healthy controls and obtained comparable accuracy rates.

Conclusions: Together, these findings identify novel neuroimaging biomarkers of active depression and depression in remission, capable of distinguishing individual patients from a pool of healthy controls with high sensitivity and specificity and replicated in an independent cohort of subjects. We also identified a potential neuronal substrate for these biomarkers in a mouse model of depression. At least three distinct processes contribute to synapse loss and abnormal spine morphology in this model: chronic stress increases the formation of new spines, decreases new spine survival, and increases the elimination of spines formed progressively earlier in development. Future studies must assess the impact of each of these processes on limbic circuit function and determine whether and how they relate to fMRI measures of functional connectivity. It is also worth noting that chronic stress effects on functional connectivity in most subjects were modest relative to the changes seen in depression, in accord with the hypothesis that deficits in resilience probably play an important role in the etiology of depression.

Keywords: depression biomarker, fMRI, dendritic spines

Disclosure: C. Liston, Nothing to Disclose; L. Grosenick, Nothing to Disclose; K. Deisseroth, Nothing to Disclose; W. Gan, Nothing to Disclose; M. Dubin, **Part 1:** Co-investigator, Clinical Medication Trial, Abbott Laboratories, Abbott Park, IL, USA, Co-investigator, Clinical Medication Trial, Otskua Pharmaceutical Development & Commercialization, Inc, Rockville, MD, USA, **Part 4:** Co-investigator, Clinical Medication Trial, Abbott Laboratories, Abbott Park, IL, USA, Co-investigator, Clinical Medication Trial, Otskua Pharmaceutical Development & Commercialization, Inc.

T194. *In Vivo* Serotonin Transporter Binding Predicts Reactivity to Emotional Conflict in Prefrontal Cortex

Julia Sacher*, Swen Hesse, Marianne Patt, Georg Becker, Franziska Moeller, Karsten Mueller, Matthias L Schroeter, Arno Villringer, Osama Sabri

Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Background: It has been shown that serotonin transporter (5-HTT) availability influences serotonin selective reuptake inhibitor (SSRI) treatment response. Variation of *in vivo* 5-HTT availability within the prefrontal cortical regions that modulate limbic reactivity to emotional stimuli is likely relevant to understanding variation in SSRI-treatment response. To address this question in a clinical population, a necessary first step is to combine an imaging method that allows for quantification of 5-HTT availability (Positron Emission Tomography, PET) with an imaging modality that provides regional information about the neural circuitry of emotional processing (functional Magnetic Resonance Imaging, fMRI) and investigate the relationship between 5-HTT availability and functional activity in the emotional processing circuit in health. In the present study, we therefore aim to establish a link between 5-HTT availability and prefrontal cortex reactivity in healthy volunteers using a multimodal imaging approach that combines both PET 5-HTT imaging and fMRI during an emotional conflict task within the same individuals.

Methods: 5-HTT-BP (binding potential) was measured using [^{11}C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-enzonitrile ([^{11}C]-DASB)-PET in 20 healthy subjects (mean age: 37 years [SD: 9 years]). A region of interest (ROI)-analysis was performed using the Logan graphical analysis method and the cerebellum for the input function. In the same subjects, we performed blood oxygenation level-dependent (BOLD) fMRI to study the neural response during an emotional conflict paradigm that is based on the presentation of emotionally congruent and incongruent face/word pairs. Regional time activity curves (TACs) were obtained in the brain regions showing BOLD response during the emotional interference experiment.

Results: All subjects showed robust behavioral interference in incongruent trials ('Stroop effect'), with a significant increase in reaction time (RT) during incongruent versus congruent trials (mean ± SD: 948 ± 141 ms versus 802 ± 119 ms, $p < 0.001$). The BOLD activation brain map during emotional incongruence versus congruence showed BOLD response in the dorsolateral prefrontal cortex (DLPFC), ($Z = 3.55$, $p < 0.001$, uncorrected, whole brain). We found 5-HTT-BP in the DLPFC to be significantly correlated with the detected fMRI BOLD response (R: 0.51, $p < 0.02$).

Conclusions: We present the first evidence from a multimodal imaging study that it is possible to link functional activity to 5-HTT availability in the prefrontal cortex, a brain region implicated in the regulation of emotion. This finding extends our understanding of the serotonin transporter, a crucial target site for antidepressant action, within the neural network that mediates the integration of emotional information to cognitive function. Direct implementation of quantitative neurochemical serotonergic imaging into current pharmaco-fMRI approaches that focus on regional aspects of drug-action will facilitate decisions in antidepressant development.

Keywords: PET, fMRI, Serotonin Transporter, Emotional Stroop Paradigm

Disclosure: J. Sacher, Nothing to Disclose; S. Hesse, Nothing to Disclose; M. Patt, Nothing to Disclose; G. Becker, Nothing to Disclose; F. Moeller, Nothing to Disclose; K. Mueller, Nothing to Disclose; M. Schroeter, Nothing to Disclose; A. Villringer, Nothing to Disclose; O. Sabri, Nothing to Disclose.

T195. The Autism Brain Imaging Data Exchange: Towards Large-scale Evaluation of the Intrinsic Brain in Autism

Adriana Di Martino*, ABIDE Consortium

NYU Child Study Center at the NYU Langone Medical Center, New York, New York

Background: The complexity and heterogeneity of Autism Spectrum Disorders (ASD) represent core challenges for the advancement of the field by limiting the ability to compare and synthesize findings across studies. In response, researchers have placed an increased emphasis on standardized assessment protocols. Simultaneously, the autism community has taken a lead role in calls for the open data sharing. Well-heeded in the genetics community, calls for sharing have gone largely unanswered in the field of neuroimaging – a tragic loss given the potential for imaging methodologies to inform our understanding of ASD. It is against

this background that the **A**utism **B**rain **I**maging **D**ata **E**xchange (ABIDE) consortium was formed to aggregate and share retrospective resting state (R)-fMRI data of individuals with ASD and age- matched typical controls (TC). Here, we aimed to demonstrate the utility of the aggregated sample for exploring the functional connectome in ASD.

Methods: *Sample.* We analyzed data from 16 sites [18 samples; 778 individuals including 361 individuals with ASD and 417 TC (age range 7-40 years; all males)]. *Strategy.* Despite overall convergence among R-fMRI studies in supporting a dysconnectivity model of ASD, reports disagree regarding the specific nature, and extent of ASD-related abnormalities in intrinsic functional connectivity (iFC) (e.g., hypo- vs. hyperconnectivity). Thus, we carried out 1) full-brain iFC analyses for both structural and functional parcellation schemes (i.e., structural: Harvard-Oxford Atlas (HOA; Kennedy et al., 1998), functional: Craddock et al., 2012 [Crad-200]); 2) regional voxel-wise measures of intrinsic functional architecture including regional homogeneity (ReHo; Zang 2004), voxel mirror homotopic connectivity (VMHC; Zuo 2011), and seed based iFC of the default network (DN; Andrews-Hanna 2010), and fractional measures of the amplitude of low frequency fluctuations (fALFF; Zuo 2010). We examined group differences using a generalized linear model, including age, FIQ, site and mean frame wise displacement (FD) as covariates. Gaussian random field theory correction for multiple comparisons was applied on statistical images with $Z > 2.3$ and cluster-level $p < 0.05$. For whole brain parcellation-wise correlation analyses, corrections for false discovery rates (FDR) (Genovese, 2002) were applied.

Results: Whole brain analyses revealed both hypo- and hyper-connectivity in ASD, though with a striking predominance of hypo-connectivity. Follow-up analyses sorting abnormal functional connections based upon different schemes (e.g., lobar, functional), showed that iFC decreases characterized temporal and frontal connections, as well as those of unimodal and heteromodal association. In constrast, hyperconnectivity was limited to subcortical regions. Consistent with prior work, reduced iFC involving key nodes in DN such as PCC and dorsomedical prefrontal cortex, as well as reduced VMHC in sensorimotor cortex characterized children with ASD. All regional analyses converged on ASD-related abnormalities in the thalamus, portions of the caudate as well as insula bilaterally.

Conclusions: The feasibility of establishing the ABIDE dataset testifies to the rapid growth of R-fMRI application to ASD and to the benefits of standardization of diagnostic assessment protocols in ASD. Evidence from this initial survey of the R-fMRI data provides demonstrations of replication (hypoconnectivty of cortico-cortical iFC and hyperconnectivity in subcortical regions) and discovery (involvement of thalamic functional architecture in ASD). In sum, bringing together multiple international datasets, the ABIDE large sample allows for replication, secondary analyses and discovery efforts, likely accelerating the pace of discovery for the next generation of studies.

Keywords: Open data sharing, autism, functional architecture, functional connectivity

Disclosure: A. Di Martino, **Part 1:** I am the coauthor of the Italian version of the Social Responsiveness Scale distributed by "Organizzazioni Speciali", thus I may receive royalties for it; ABIDE Consortium, Nothing to Disclose.

T196. The Efficacy of an Adenovirus-based Anti-cocaine Vaccine to Reduce Cocaine Self-administration in Rhesus Monkeys Using a Choice Procedure

Suzette M. Evans*, Richard W. Foltin, Martin J. Hicks, Jonathan B. Rosenberg, Bishnu P. De, Kim D. Janda, Stephen M. Kaminsky, Ronald G. Crystal

New York State Psychiatric Institute and Columbia University, New York, New York

Background: Cocaine is a major public health problem. Traditional pharmacotherapy approaches have been unsuccessful to date, with no FDA-approved pharmacological treatments for cocaine dependence. Immunotherapy offers a novel approach for treating cocaine abuse by specifically targeting the drug and preventing its access to the CNS. In a previous study, rats vaccinated with a cocaine vaccine, dAd5GNE, had long-lasting, high anti-cocaine antibody titers, effecting decreases in: (1) the reinforcing effects of self-administered cocaine; (2) "extinction burst" responding; and (3) post extinction cocaine-seeking behavior due to a cocaine "prime" (Wee et al, Neuropsychopharmacology 2012). The goal of this study was to extend and validate these findings of dAd5GNE vaccine efficacy in non-human primates using a choice procedure to measure the reinforcing effects of cocaine.

Methods: Six experimentally naïve adult female rhesus monkeys (*Macaca mulatta*), weighing 4.5 to 8.3 kg, were separately housed unrestrained in 2 connected non-human primate cages. All study procedures and aspects of animal maintenance complied with the US National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by the New York State Psychiatric Institute Animal Care and Use Committee. Monkeys were initially trained to climb into and sit in non-human primate chairs and respond for candy on a fixed ratio schedule. Then monkeys were surgically implanted with a chronic indwelling catheter that terminated in a subcutaneous vascular access port (VAP) for long-term intravenous drug administration. Monkeys were trained to self-administer 0.1 mg/kg/injection of cocaine; when monkeys reliably self-administered cocaine, a 10-trial choice procedure was introduced. The final choice schedule was FR25 for 0.1 mg/kg/injection of cocaine on one lever and FR5 for 10 candies (except one monkey was on a FR5 for cocaine and FR1 for candy) on an alternate lever. At the beginning of each trial, the first response on either the cocaine or candy lever determined the commodity available for that trial. Each trial was independent, with an inter-trial interval of 3 min. After baseline responding for cocaine and candy was established using the choice procedure, 4 monkeys received active vaccine and 2 monkeys received vehicle intramuscularly in a 0.5 ml volume. The cocaine vaccine used a disrupted serotype 5 adenovirus (Ad) gene transfer vector coupled to a third-generation cocaine hapten, termed GNE (dAd5GNE). Boosts were administered and serum antibody titers measured periodically throughout the study. Choice behavior during self-administration, extinction and reinstatement sessions was measured.

Results: Before vaccine or vehicle administration, all 6 monkeys preferentially self-administered cocaine over candy. Serum anti-cocaine antibody titers in the 4 vaccinated animals increased and remained elevated for the entire study, while levels in the 2 control animals remained below the limit of detection. There was no change in the choice of cocaine over candy over a 20 wk period in 5 of the 6 monkeys, although one of the vaccinated monkeys did switch her choice from cocaine to candy at 12 wk after initial vaccination and this choice remained through wk 20 post-initial vaccination, when the saline extinction phase began. All 6 monkeys extinguished responding for cocaine during the extinction phase, with no clear differences between vaccinated and control monkeys. Priming doses of cocaine (0.1 or 0.3 mg/kg) failed to increase the number of cocaine choices during saline extinction. Vaccination substantially retarded reinstatement when cocaine was again available for self-administration. The 2 control monkeys and 1 vaccinated monkey reinstated cocaine self-administration within 4-40 sessions. The other 3 vaccinated monkeys failed to reinstate cocaine self-administration even upon repeated priming with cocaine. When the FR was reduced and/or the alternative candy lever was unavailable, there was still no evidence for cocaine reinstatement in the 3 monkeys. Lastly, for 2 of the 3 vaccinated monkeys the dose of cocaine available for self-administration was increased to 0.2 mg/kg/infusion under a low FR requirement. Under these conditions, both monkeys eventually switched their choices from candy to cocaine, but only after a total of 50-90 reinstatement sessions.

Conclusions: Overall, these data indicate that the dAdGNE vaccine can block cocaine reinstatement after extinction in non-human primates and thus has therapeutic potential for humans, particularly within the context of a relapse prevention strategy paired with

the availability of alternative reinforcers. Supported by grants RC2 DA028847 (SME, JBR, BPD, KDJ, SMK, RGC), T32 HL094284 (MJH), and K05 DA031749 (RWF).
Keywords: Cocaine Vaccine Rhesus monkeys Self-administration Reinstatement
Disclosure: S. Evans, Nothing to Disclose; R. Foltin, Nothing to Disclose; M. Hicks, Nothing to Disclose; J. Rosenberg, Nothing to Disclose; B. De, Nothing to Disclose; K. Janda, Nothing to Disclose; S. Kaminsky, Nothing to Disclose; R. Crystal, Nothing to Disclose.

T197. Controlled Trial of Cognitive Remediation in Psychotic Bipolar Disorder: Feasibility, Tolerability, and Development of a Web-based Computer Control

Kathryn E. Lewandowski*, Bruce Cohen, Sarah Sperry, Dost Ongur, Matcheri Keshavan

McLean Hospital/Harvard Medical School, Belmont, Massachusetts

Background: Cognitive dysfunction is increasingly recognized as a major lifelong feature of Bipolar Disorder (especially BD I with psychosis; PBD) - present by illness onset, persistent into euthymia, and strongly associated with functional outcomes. Computer-based cognitive remediation (CR) has shownpromise in improving cognitive and functional outcomes in patients with SZ. However, despite the similarities of neurocognitive deficits between patients with SZ and PBD, few studies have extended neuroscience-based CR to patients with PBD. Additionally, this study is the first we are aware of to employ a web-based approach to CR, necessitating the development of a comparable web-accessible control paradigm. *Aims:* We aimed in this preliminary study to a) describe the development of our control condition and b) to assess feasibility and tolerability of the CR and control conditions.
Methods: PBD patients (n = 29) were randomized to either CR (n = 16) or an active computer control (n = 13). Both conditions involved 70 sessions (3 per week for 24 weeks). Participants were required to attend 1 session per week at the study site; 2 sessions could be completed at the study site or remotely. CR treatment used BrainWorks, a web-based CR system chosen because of its neuroplasticicy-based, bottom-up training protocol which has been shown to be effective in patients with schizophrenia. The control condition was developed to be similar to the treatment condition in format, butwithout the neuroplasticity-based, bottom-up approach to cognitive training.
Results: a) *Development of the Computer Control:* Sessions involve generic games administered via the online interface Sporcle, which offers a collection of thousands of quiz-type activities. We carefully selected several hundred games and rated them on difficulty based on available data documenting accuracy rates of thousands of online users. Selected games were divided into 70 sessions of prescribed activities in order to mirror the structure of the treatment condition. An administrator account allows study staff to track subject activity to confirm adherence. To date, no subject has indicated that they are aware of their treatment condition to any study staff member. b) *Feasibility and Tolerability:* All subjects chose to attend only the mandatory session per week at McLean. Completion rates, total sessions attended, and assessments completed did not differ by condition. 71% of subjects completed their post-treatment assessment (CR = 69%; Control = 75%). Within completers, subjects completed an average of 67 of 70 sessions (96%); sample-wide, subjects completed an average of 53 sessions (76%; this includes one outlier who completed only 4 sessions). 90% of subjects completed at least one post-baseline assessment. 23% of dropouts were due to acute symptom exacerbation/hospitalization; 9% were due to the time commitment of the study.
Conclusions: The present study is the first we are aware of to implement neuroplasticity-based computer CR in patients with PBD, and the first study we are aware of using web-based CR treatment and newly developing a comparable on-line computer-based control paradigm. Adherence rates were high in both groups, and double-blindness of intervention type was successfully maintained. Computer-based CR appears to be both feasible and tolerable in patients with PBD. The online format allows engaging in treatment that is more accessible than multiple on-site visits weekly, while still providing staff contact and bridging opportunities. As the study progresses, we will evaluate the efficacy of CR compared to an active computer control in patients with PBD. As cognitive deficits are strongly associated with functional outcomes in patients with PBD, CR provides an opportunity to target this key symptom domain.
Keywords: bipolar disorder psychosis cognitive remediation neuroplasticity
Disclosure: K. Lewandowski, **Part 1:** I am a consultant for Clintara, **Part 2:** Clintara; B. Cohen, Nothing to Disclose; S. Sperry, Nothing to Disclose; D. Ongur, **Part 2:** Assoc Editor for Archives of Gen Psychiatry, CME lectures for New England Educational Institute, **Part 4:** PI on a research contract with Rules Based Medicine; M. Keshavan, **Part 1:** Lecture honorarium-Otsuka in 2012, **Part 4:** Grants by GSK and Sunovion since 2010.

T198. Exercise Improves Physical Capacity in Obese Patients with Schizophrenia: Pilot Study

Martin T. Strassnig*, John W. Newcomer, Philip Harvey

University of Miami, Miami, Florida

Background: Aim of this feasibility study was to determine effects of and adherence to a brief cardiovascular fitness intervention aimed at improving physical capacity in obese patients with schizophrenia.
Methods: Obese individuals with DSM-IV schizophrenia were eligible to participate. Eight individuals were screened for participation. Two cited inconvenient time, interfering with other pursuits, as reasons for non-participation. The six remaining participants (recruitment goal, n = 6) exercised on treadmills at the University of Miami Clinical Research Center for 6 weeks, three times a week, under supervision of our research assistant. We measured changes in body weight (BMI), physical capacity (submaximal exercise test, 6 minute walk test), habitual physical activity (pedometer) and health-related quality of life (MOS Short form 36). In addition, at baseline, Intrinsic motivation inventory (IMI) was completed.
Results: Among the 4 male and 2 female participants, average age was 36.8 ± 10.4 years and n = 5 were smokers. Participants smoked 15.3 ± 11.7 cigarettes/day. Diagnosis was chronic paranoid schizophrenia (n = 4) or schizoaffective disorder (n = 2). Resting heart rate decreased (96.3 ± 19 vs. 84.8 ± 21.3; Z = −2.2, *p = 0.027*). Physical capacity (VO2max ml/kg/min) increased (26.5 ± 5.4 vs. 31 ± 4.4 ml/kg/min; Z = −2.1, *p = 0.028*) (Fig 1). MCS as derived from the SF-36, improved (38.9 ± 9.5 vs. 52.1 ± 7.4; Z = −2.2, *p = 0.028*). Waist circumference decreased (43.6 ± 5 vs. 42 ± 4.5 in; Z = −2.02, *p = 0.043*). There were no significant changes in BMI (35.1 ± 3.8 vs. 33.2 ± 3.2; Z = 1.6, *p = 0.08*) or body weight (231.5 ± 44.2 vs. 226.5 ± 43.3 lbs; Z = −1.76, *p = 0.08*). Session adherence was 85.3 ± 15.1 %. No adverse events occurred.
Conclusions: The 6 week cardiovascular exercise program led to a 17% improvement in cardiovascular fitness on average (change in VO2max ml/kg/min), and significantly improved quality of life. Designed for practical use, the program was administered by a research assistant without specialized prior experience, and required modest time commitment and few resources, aside from treadmills.
Keywords: schizophrenia, obesity, cardiovascular fitness, physical capacity
Disclosure: M. Strassnig, Nothing to Disclose; J. Newcomer, Nothing to Disclose; P. Harvey, **Part 1:** Abbott Labs, Amgen, Boeheringer Ingelheim, Bristol-Myers-Squibb, Forest Labs, Genentech, Johnson and Johnson, Pharma Neuroboost, Roche Pharma, Shire Pharma, Sunovion Pharma, Takeda Pharma, **Part 4:** AstraZeneca.

T199. Is Repetitve Transcranial Magnetic Stimulation Effective in Treatment Resistant Depression? A Systematic Review

Bradley N. Gaynes*, Stacey Lloyd, Linda Lux, Gerald Gartlehner

Univeristy of North Carolina School of Medicine, Chapel Hill, North Carolina

Background: Patients with two or more prior antidepressant treatment failures, often referred to as having treatment resistant depression (TRD), have a decreased likelihood of recovery with subsequent medication treatment. In this case, nonpharmacologic treatments, such as repetitive transcranial magnetic stimulation (rTMS), are often considered.
Methods: As part of a larger comparative effectiveness review on nonpharmacologic interventions for TRD, we searched MEDLINE, Embase, the Cochrane Library, PsycINFO, and the International Pharmaceutical Abstracts. For this analysis, studies comparing repetitive transcranial magnetic stimulation (rTMS) to sham or control treatment were included. Using a standard protocol, we abstracted data on patient population, outcomes (severity of depressive symptoms, response rate, remission rate), settings, funding, study design, and risk of bias for each study.
Results: rTMS was beneficial relative to controls receiving a sham procedure for all three outcomes. rTMS produced a greater decrease in depressive severity (high strength of evidence). Specifically, rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points relative to sham control, and this change meets the minimum threshold of the 3-point HAM-D difference that is considered clinically meaningful. Response rates were greater with rTMS than sham (also high strength of evidence); those receiving rTMS were more than three times as likely to achieve a depressive response as patients receiving a sham procedure. Finally, rTMS was more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving rTMS were more than six times as likely to achieve remission as those receiving the sham.
Conclusions: For depressed patients with two or more antidepressant treatment failures, rTMS is a reasonable consideration.
Keywords: treatment resistant depression, rTMS, systematic review
Disclosure: B. Gaynes, Nothing to Disclose; S. Lloyd, Nothing to Disclose; L. Lux, Nothing to Disclose; G. Gartlehner, Nothing to Disclose.

T200. Functional Connectivity of Attention Network Relates to Drink Volume in Youth

Barbara Weiland*, Robert Welsh, Mary Soules, Crosby Modrowski, Robert Zucker, Jon-Kar Zubieta, Mary Heitzeg

University of Colorado, Boulder, Colorado

Background: The transition years from adolescence to adulthood are associated with high levels of alcohol and drug use concurrent with dynamic neuromaturation. For example, later maturation of top-down control systems is hypothesized to influence reward response resulting in risky behaviors, including drinking, during this age range. Furthermore, connectivity studies have shown the brain develops into progressively specialized systems including the Frontoparietal Control, Attention, and Default Mode networks. Studies in adults have additionally shown functional connectivity to be altered with alcohol and other drug use. We hypothesized that high drinking young adults would have increased response to reward and less developed Attention and Control networks compared to low drinkers.
Methods: 99 right-handed 18-25 year olds were recruited from the ongoing Michigan Longitudinal Study. The subjects performed a modified monetary incentive delay task during functional magnetic resonance imaging (fMRI). Low and High drinking groups ($n = 49/50$) were created based on lifetime drink volume. Statistical parametric mapping was used to model incentive anticipation and create individual task activation maps. Task data was then concatenated for functional connectivity analysis. Frontoparietal, Attention, and Default networks were identified using previously defined nodes. Correlation matrices between nodes of each network were calculated and transformed to z-scores. Group differences in task activation and functional connectivity were tested using independent sample *t*-tests.
Results: The low and high drinking groups did not differ in task performance but the high drinkers exhibited more activation in bilateral nucleus accumbens for large reward and loss anticipation. The high drinking group had significantly lower connectivity between left frontal eye field, in the prefrontal cortex, and left superior parietal lobule (LFEF-LSPL) nodes in the Attention network. LFEF-LSPL connectivity was negatively correlated with attention problems, and delinquent and externalizing behaviors across all participants.
Conclusions: The increased striatal anticipatory response in the high drinkers may represent increased sensitivity to reward. Reduced LFEF-LSPL connectivity was associated with risk-related behaviors and may reflect inefficient top-down regulation by the Attention network. These results suggest that altered functional connectivity in high alcohol consuming young adults may play a role in the underlying pathology of addiction.
Keywords: Substance abuse, fMRI, functional connectivity, reward, attention
Disclosure: B. Weiland, Nothing to Disclose; R. Welsh, Nothing to Disclose; M. Soules, Nothing to Disclose; C. Modrowski, Nothing to Disclose; R. Zucker, Nothing to Disclose; J. Zubieta, Nothing to Disclose; M. Heitzeg, Nothing to Disclose.

T201. Comparison of the Neurocognitive Effects between Acute Course Magnetic Seizure Therapy and Electroconvulsive Therapy: A Preliminary Report

Shawn M. McClintock*, Mustafa M. Husain, C. Munro Cullum, Bruce Luber, Paul Croarkin, Angel Peterchev, Kenneth Trevino, Mohamed Aly, Louis Stool, Ahmad Raza, Sarah Lisanby

UT Southwestern Medical Center, Dallas, Texas

Background: Neurotherapeutic interventions are presently in development for the treatment of major affective disorders. One such novel technique is magnetic seizure therapy (MST), which uses magnetic pulses to induce a therapeutic convulsive seizure. This strategy capitalizes upon the established safety of transcranial magnetic stimulation (TMS) and antidepressant efficacy of tonic-clonic seizures as induced with electroconvulsive therapy (ECT). MST is hypothesized to be a safe and effective antidepressant strategy for patients with major affective disorders. Indeed, preclinical and clinical evidence has substantiated that MST produces little to no physiological or neurocognitive adverse effects. Also, clinical evidence in the form of case reports and series, as well as controlled clinical trials, has documented decreased depression severity after an acute MST course. To date, studies with MST stimulus doses with up to 600 pulses have been reported, and there is limited data regarding its safety when administered at higher doses (e.g., 1000 pulses). Increasing the number of stimulus pulses improves the antidepressant efficacy in ECT, and a similar trend may exist in MST. However, evidence from ECT studies clearly show that higher doses may result in increased adverse neurocognitive effects. Therefore, information regarding MST administration at higher doses is critical to guide the development of this intervention, and inform its safety profile. Thus, the purpose of this study was to compare the neurocognitive effects of high-dose MST and standard ECT in patients with a current major depressive episode.
Methods: This was a three-center, between-subject, randomized, double-masked controlled clinical trial that compared the neurocognitive effects of high dose MST and ultra-brief pulse RUL ECT. All participants provided written informed consent for this IRB approved investigation before completing study procedures. The study was conducted under a US FDA IDE. Adults with a major

depressive episode in the context of unipolar or bipolar depression, based on the SCID-I, were randomly assigned to treatment with MST or ECT. For MST, a Magstim Theta device with a round coil positioned on the vertex was used to administer the stimulus. Seizure threshold was titrated at the first session by incrementing the train duration, and subsequent treatments were provided at maximal device output (100% maximal pulse amplitude, 100 Hz pulse repetition frequency, 10 second (1000 pulses) train duration). For ECT, treatments were provided via standard RUL electrode configuration, 800 mA pulse amplitude, and ultra-brief pulse width (0.3 ms). Seizure threshold was titrated at the first session by incrementing the train duration and frequency, and subsequent treatments were provided at 6′ the seizure threshold charge. Patients were treated until they achieved remission (<8 on the 24-item Hamilton Rating Scale for Depression) or received a maximum of 14 MST or ECT sessions. To assess neurocognitive effects, we used a comprehensive battery of standard measures to assess domains of global cognitive function, processing speed, attention, anterograde learning and memory, retrograde memory, and executive function. Trained neuropsychometricians, masked to treatment condition, administered the neurocognitive battery before and after the acute treatment course. Raw scores on each neurocognitive measure were converted into demographic-adjusted standard scores. Summary statistics were used to describe the sociodemographic and clinical characteristics of the study cohort. Means and standard deviations are presented for continuous variables; percentages are presented for discrete variables. Repeated-measure ANCOVAs were computed for each neurocognitive variable with time point (baseline, end) as the repeated factor, treatment condition (MST, ECT) as the between-subject factor, and study center as the covariate. Post-hoc analyses were computed for significant main effects or interactions. Statistical significance was defined as a two-sided p-value of less than 0.05.

Conclusions: This study contributes to an emerging body of evidence regarding the development of magnetic seizure therapy as a novel neurotherapeutic intervention for the treatment of major affective disorders.

Keywords: magnetic seizure therpy, electroconvulsive therapy, neuropsychology, depression, transcranial magnetic stimulation

Disclosure: S. McClintock, **Part 1:** Consultant to Shire Pharmaceuticals; M. Husain, **Part 1:** Research support from Magstim, Inc., Cyberonics Inc., NeoSync, Inc., Brains Way, Inc., St. Jude Pharmaceutical, Dey Pharma, Inc., Neuronetics, Inc., **Part 4:** Dey Pharma, Inc; C. Cullum, Nothing to Disclose; B. Luber, Nothing to Disclose; P. Croarkin, **Part 4:** Research support from Pfizer Inc; Served as a site sub- or principal investigator (without additional compensation) for Eli Lilly and Co, Indianapolis, Indiana; Forest Laboratories Inc, New York, New York; Merck and Co Inc, Whitehouse Station, New Jersey; and Pfizer Inc.; A. Peterchev, **Part 1:** Inventor on patents and patent applications related to TMS and MST technology assigned to Columbia University or Duke University; inventor on patents and patent applications on TMS licensed to Rogue Research; received patent royalties (through Columbia) and a research grant (through Duke) from Rogue Research and equipment donations from Magstim, MagVenture, and ANS/St. Jude Medical; K. Trevino, Nothing to Disclose; M. Aly, Nothing to Disclose; L. Stool, Nothing to Disclose; A. Raza, Nothing to Disclose; S. Lisanby, **Part 1:** Research support from Magstim, Inc., NeoSync, Inc., Brains Way, Inc., St. Jude Pharmaceutical, Inc., Neuronetics, Inc.

T202. Electroconvulsive Therapy Potentiates the Inhibition of Gamma Oscillations in Treatment Resistant Depression

Mera S. Barr*, Lakshminarayan V. Chinta, Natasha Radhu, Marina V. Frantseva, Daniel M. Blumberger, Andrea J. Levinson, Zafiris J. Daskalakis

University of Toronto Centre for Addiction and Mental Health, Toronto, Ontario, Canada

Background: Electroconvulsive therapy (ECT) remains the treatment of choice for patients with treatment resistant depression (TRD). ECT may exert its therapeutic effects through the potentiation of cortical inhibition known to be reduced in patients with TRD. Cortical inhibition is a neurophysiological mechanism in which γ-aminobutyric acid (GABA) inhibitory interneurons selectively attenuate the activity of pyramidal neurons in the cortex. Cortical inhibition can be measured directly from the motor cortex using transcranial magnetic stimulation (TMS) and concurrent electroencephalography (EEG). This technique allows for the examination of specific oscillatory frequencies such as the gamma band (30-50 Hz) whose modulation may be related to cortical inhibition deficits mediated by GABAergic inhibitory mechanisms. The primary objective of this study was to evaluate whether the potentiation of cortical inhibition is mechanistically linked to the treatment effects of ECT in TRD. The secondary objective was to examine how ECT influences the inhibition of specific oscillatory frequencies measured from the motor cortex in TRD.

Methods: Cortical inhibition was measured with TMS-EEG from the left motor cortex within 48 hours prior to- and following an acute ECT treatment course in thirteen patients with TRD. Pre and post motor cortical inhibition in patients with TRD were then compared to a group of 21 healthy subjects who were evaluated in a single session.

Results: Prior to ECT, deficits in overall (1-50 Hz) cortical inhibition were found in patients with TRD compared to healthy subjects ($p = 0.0164$). Examination of specific oscillatory frequencies revealed that the inhibition of gamma oscillatory activity contributed significantly to the group difference ($p = 1.93e-07$). Following ECT, gamma inhibition was significantly potentiated from baseline values in patients with TRD ($p = 0.0029$) and normalized to values comparable to healthy subjects ($p = 0.2793$).

Conclusions: These findings suggest that potentiation of gamma cortical inhibition may represent a unique mechanism through which ECT exerts its therapeutic effects in patients with TRD.

Keywords: Electroconvulsive therapy, treatment-resistant depression, cortical inhibition, transcranial magnetic stimulation, electroencephalography

Disclosure: M. Barr, Nothing to Disclose; L. Chinta, Nothing to Disclose; N. Radhu, Nothing to Disclose; M. Frantseva, Nothing to Disclose; D. Blumberger, Nothing to Disclose; A. Levinson, Nothing to Disclose; Z. Daskalakis, Nothing to Disclose.

T203. Changes in Default Mode Resting State fMRI Following ECT in Major Depression

Georgios Petrides*, Miklos Argyelan, Styliani Kaliora, Philip R. Szeszko

The Zucker Hillside Hospital, Northsore-LIJ Health System, New York, New York

Background: Althoughelectroconvulsive therapy (ECT) is a highly effective treatment for major depression, little is known regarding its underlying mechanism of action. In the last decade novel fMRI techniques have become available to measure and evaluate functional connectivity and brain networks. Several previous studies indicated that fronto-limbic connections and more specifically the default mode network play a critical role in mood regulation, but studies are critically needed to evaluate whether these structures are involved in treatment response in ECT.

Methods: To date four patients (2 males, 2 females, age: 40.5 ± 11.2 y) referred for ECT were included in this preliminary study. Inclusion criteria were diagnosis of a major depressive episode without psychotic features confirmed by SCID-IV interview, and a Hamilton Rating Scale for Depression (HRSD24) $\geqslant$ 21. Patients with a diagnosis of psychotic and neurological disorders, as well as substance abuse or dependence were excluded. Patients received ECT with standard bifrontal electrode placement at 50% above seizure threshold 3 times per week until they remitted or were declared non-responders. Remission was defined as 3

consecutive ratings of HRSD24 < 10. Standard ECT procedures were followed and HRSD24 evaluations were performed before each ECT treatment. For resting state fMRI patients underwent 4 runs of 5 minutes each with eyes closed. The timeline included: (1) within 24 hours before the first ECT (baseline); (2) within 36 hours after the first ECT and (3) within 36 hours after the last ECT. Scans were acquired on a 3T GE MRI machine. We used an independent component-dual regression analysis with predefined templates to analyze the resting state fMRI data.
Results: The default mode network showed significant modulation by ECT with gradually decreasing expression values from baseline (1st time-point) to the 3rd time-point. Further analysis showed that down-regulation of this network did not necessarily indicate the attenuation of the network. Statistical parametric mapping (SPM) analysis of the default mode network showed several significant bilateral increases (FDR corrected, $p < 0.05$), but no reductions in activity. Fast Fourier transformation of the images revealed that ECT also abolished slow wave activity in subcallosal cingulate cortex, and that this finding was robust across subjects.
Conclusions: Our data suggest that changes in the default mode network and subcallosal cingulate cortex, which are hypothesized to play an important role in affect regulation, occur following ECT for depression. The down-regulation of the default mode network observed in our study may be the result of new or *a priori* less active areas (e.g., lateral parietal, insula and lateral prefrontal) becoming part of the default mode network, which warrants further investigation. Moreover, our findings have implications for further research seeking to elucidate the mechanisms of action of ECT and the underlying biological substrate of depression.
Keywords: Electroconvulsive therapy, fMRI, resting state, default mode network, depression
Disclosure: G. Petrides, Nothing to Disclose; M. Argyelan, Nothing to Disclose; S. Kaliora, Nothing to Disclose; P. Szeszko, Nothing to Disclose.

T204. Prefrontal rTMS Versus tDCS Effects on Perceived Controllability and the Emotional Dimension of Pain: Implications for Mechanisms of Technology-specific Action

Jeffrey J. Borckardt*, Scott Reeves, Alok Madan, Jennifer Naylor, Sarah Fredrich, Heather Frohman, Kelly Barth, Mark S. George

Medical University of South Carolina, Charleston, South Carolina

Background: The prefrontal cortex may be a promising target for transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) in the management of depression and pain. It is not clear how prefrontal TMS affects pain perception, but previous findings suggest that ventral lateral and medial prefrontal circuits may comprise an important part of a circuit of 'perceived controllability' regarding pain, stress and learned helplessness. It has been demonstrated that when one has the perception of control over a painful stimulus, it is experienced as less painful than when one believes the pain to be uncontrollable. While the left dorsolateral prefrontal cortex (DLPFC) is a common TMS and tDCS target for treating clinical depression as well as modulating pain, little is known about whether stimulation of this area may directly affect perceived controllability. The present study explored the immediate effects of fast TMS and tDCS over the left DLPFC on the analgesic benefits associated with perceived pain controllability.
Methods: In two separate studies, a total of sixty-five healthy volunteers underwent a laboratory pain task designed to manipulate perception of pain controllability under conditions of real versus sham 10 Hz rTMS, or 2 mA anodal versus cathodal tDCS over the left dorsolateral prefrontal cortex.
Results: Real TMS over left DLPFC, compared to sham, produced the same magnitude of analgesic benefit associated with perceived-control on the emotional dimension of pain, but significantly decreased subjective perceptions of perceived controllability. Anodal tDCS was associated with only modestly enhanced analgesic benefit of perceived control, but was associated with significantly higher ratings of subjective perceived control over pain. Cathodal tDCS of the left DLPFC increased pain unpleasantness ratings and disrupted the analgesic benefits of the perceived controllability of pain than cathodal stimulation.
Conclusions: Taken together, these findings suggest that TMS may be capable of taking-over the perceived-controllability circuit exogenously, mimicking the analgesic benefit of perceived control, but taking away subjects' sense of volition and/or perceptions of enhanced controllability, whereas, anodal tDCS enhances subjects' volitional sense of perceived controllability while only modestly boosting the analgesic benefit of perception of control. Thus, TMS appears to commandeer neural circuits, effectively running them for participants, while tDCS enhances participant's potential to volitionally enhance neural circuit effectiveness.
Keywords: TMS, tDCS, pain, prefrontal cortex, perceived control
Disclosure: J. Borckardt, Nothing to Disclose; S. Reeves, Nothing to Disclose; A. Madan, Nothing to Disclose; J. Naylor, Nothing to Disclose; S. Fredrich, Nothing to Disclose; H. Frohman, Nothing to Disclose; K. Barth, Nothing to Disclose; M. George, Nothing to Disclose.

T205. Oxytocin Differentially Decreases Methamphetamine Intake and Reinstatement to Methamphetamine Seeking in Male and Female Rats

Carmela M. Reichel*, Brittney Cox, Amy Young, Ronald E. See

Medical University of South Carolina, Charleston, South Carolina

Background: Notable sex differences exist in methamphetamine (meth) addiction patterns; however, meth effects and potential therapeutic treatments have typically only been studied in males. Oxytocin may be an effective pharmacotherapeutic agent for meth addiction. Here, we determined whether oxytocin impacted motivation for meth self-administration as well as its efficacy at reducing reinstatement in both males and freely cycling females.
Methods: Rats self-administered meth or sucrose pellets (FR5 schedule of reinforcement). Following stable daily meth or sucrose intake, rats were tested on a progressive ratio after acute oxytocin (1 mg/kg) or saline. Lever responding was then extinguished and rats underwent a series of conditioned cue, meth, and yohimbine primed reinstatement tests with oxytocin (1 mg/kg) or saline.
Results: On the progressive ratio test, females showed a marked increase in lever responding, drug infusions, and break points relative to males. Oxytocin effectively decreased responding on these measures only in females. Further, this sex difference was specific to meth, as sucrose intake in males and females did not differ on any measure, nor did oxytocin impact responding. Females reinstated more than males to meth-conditioned cues and oxytocin decreased responding in females only. Females had greater meth-primed reinstatement and oxytocin decreased meth seeking in both sexes. Oxytocin did not affect reinstatement of sucrose seeking under any conditions.
Conclusions: Oxytocin displayed both meth and sex specific effects on motivated meth intake and reinstatement to meth seeking. Oxytocin decreased meth-primed, but not sucrose-primed reinstatement, indicating specificity for meth over a natural reward. In meth females only, oxytocin decreased motivation to obtain meth and responding in the presence of conditioned meth cues. In general, these data suggest that oxytocin may be a potential treatment for prevention of relapse in meth addiction for males and females with more extensive benefits in females.
Keywords: methamphetamine, sex differences, oxytocin, relapse, self-administration
Disclosure: C. Reichel, Nothing to Disclose; B. Cox, Nothing to Disclose; A. Young, Nothing to Disclose; R. See, Nothing to Disclose.

T206. Maternal Experience Affects Drug Abuse Vulnerability in the Female Rat

Jennifer Cummings*, Jill B. Becker

University of Michigan, Ann Arbor, Michigan

Background: Maternal experience is a factor that significantly alters neurological and behavioral development of the offspring. Interestingly, maternal experience also results in a number of positive effects on the mother, such as increased memory and enhanced spatial ability, which persist well after the offspring have been weaned. Because the brain areas and neural circuitry that are heavily involved in mediating maternal care are the same as those activated by drugs of abuse, we have begun to examine the effect of prior motherhood on drug abuse liability.

Methods: First, we evaluated differences in drug taking between nulliparous (virgin) and primiparous females (those that have given birth to and reared one litter), using a variety of self-administration paradigms. Using a low dose of cocaine (0.4 mg/kg/infusion), we first trained the animals to self-administer cocaine on a fixed ratio 1 (FR1) schedule. We next examined the number of infusions the animals would take when the drug was easy to obtain (i.e., FR5), after which we examined how hard the animals would work for cocaine by increasing the number of nose pokes required to obtain an infusion in subsequent sessions (up to an FR175). To see if there would be an effect of maternal experience on responding in the face of adverse consequence, we paired an infusion of cocaine with a foot shock and compared the number of infusions obtained. Finally, in order to evaluate the animals' neurological responses to cocaine, we used *in vivo* microdialysis to examine cocaine-induced dopamine release in the nucleus accumbens (NAc) after an injection of cocaine (10 mg/kg, IP) in drug-naïve nulliparous and primiparous rats. All experimental procedures were approved by the University's Committee on Use and Care of Animals and were conducted in accordance with the National Institute of Health's *Guide for the Care and Use of Laboratory Animals*.

Results: When self-administering cocaine on the FR1 schedule, nulliparous females demonstrate escalation (that is, increase drug taking) during the first week whereas primiparous females maintain a steady level of responding. Additionally, when cocaine is challenging to obtain (i.e., FR70 or higher), nulliparous females will work harder than primiparous females to obtain an infusion of the drug. While there are no differences between the groups in number of responses when cocaine is paired with the foot shock, we do find that the primiparous females self-administer more cocaine following the foot shock exposure when cocaine is offered on a FR5 schedule. In terms of the neurochemical response, drug-naïve nulliparous females release significantly more dopamine in the NAc in response to cocaine than do primiparous females. After exposure to cocaine, however, there are no effects of maternal experience on cocaine-induced DA release in the NAc.

Conclusions: We found that prior maternal experience alters a female rat's response to cocaine in a way that attenuates her drug abuse liability by making her less susceptible to the effects of cocaine. This is the first time that experiments have been conducted to examine the effect of reproductive experience on cocaine vulnerability. Females who have been mothers had reduced cocaine-induced dopamine release in the NAc, a change that may underlie the decreased rewarding value of cocaine for primiparous rats. An attenuated desire for drug may prevent the animal from progressing into repeated or habitual drug taking. After the animals have self-administered cocaine for multiple weeks, the amount of dopamine released in response to cocaine is no longer different between primiparous and nulliparous females. As this response is different from drug-naïve animals, this finding indicates that the maternal brain responds differently to self-administered cocaine than does the non-maternal brain. While primiparous females take more cocaine on the FR5 schedule, this effect is seen after experiencing a stressor (i.e., the foot shock). Consequently, maternal experience may interact with the stress response to affect drug taking in a way that has not yet been determined. We do not know at this time if the effects we report here are a result of the pregnancy (and the hormones to which the female is exposed at that time), or if the effects are driven by the experience of caring for young. Future experiment will be aimed at delineating these effects. Our findings that maternal experience affects drug abuse vulnerability are novel, exciting, and important, and have significant implications with respect to translational research in humans, as women who are mothers may also exhibit significantly different neurological and behavioral responses to drug than those females who are not mothers.

Keywords: Cocaine; Motherhood; Reward; Self-administration

Disclosure: J. Cummings, Nothing to Disclose; J. Becker, Nothing to Disclose.

T207. Phenotypic Heterogeneity Reduces the Power of Genome-wide Association Studies

Martin Alda*, Jeff Cullis, Mirko Manchia, Rudolf Uher

Dalhousie University, Halifax, Nova Scotia, Canada

Background: Findings from genome wide association studies (GWAS) of psychiatric disorders have identified genetic risk variants that explain only a fraction of the total phenotypic variance. Researchers have hypothesized that part of the missing heritability of complex diseases could be attributed to yet undetected rare risk variants with larger effect sizes than common variants. Alternatively, the inconsistent GWAS findings could be caused by phenotypic (and genetic) heterogeneity of studied traits.

Methods: In Study 1 we simulated case-control data with increasing (up to 90%) phenotypic admixture in cases. For each level of admixture, we calculated the sample size needed to achieve 90% statistical power to detect association at $p \leqslant 5 \times 10^{-8}$. Simulations were performed under different genotype relative risks (1.1, 1.2, 1.3, 1.5, 2.0, 5.0), for varying population prevalence (0.001, 0.01, 0.05, 0.1), under dominant and multiplicative genetic models. For each combination of parameters we generated 10,000 replicates of the data. In Study 2 we analyzed Welcome Trust case Control Consortium (WTCCC) data on diabetes mellitus type 1 (DM1) and 2 (DM2). For each phenotype we replaced varying proportions of cases from the other phenotype group. The analyses were restricted to the top 20 SNPs in WTCCC original report for both DM1 and DM2.

Results: In Study 1, heterogeneity decreased significantly the statistical power that was disproportionately larger than the degree of admixture: increase in a proportion of "non-cases" resulted in a non-linear increase of the sample size needed to achieve 90% of statistical power. For instance, admixture set at 50% required at a minimum three times the sample size needed to achieve the same statistical power without admixture. Heterogeneity caused a marked reduction of the estimated effect size reflected in decrease of estimated odds ratios. This effect size reduction was also non-linear in relation to the degree of admixture. Similarly, in Study 2, the presence of admixture (proportion of DM1 cases among DM2 and vice versa) also reduced substantially the significance of the observed association. For instance, at admixture level of 0.3 only 3 out of 28 originally significant or suggestive associations for DM2 had p values of $<10^{-4}$. For DM1 only three SNPs remained significant and 5 suggestive at $p<10^{-4}$.

Conclusions: Our findings confirm the impact of phenotypic heterogeneity on GWAS findings. The accuracy of phenotypic assessments and the use of *a priori* defined subgroups such as responders to lithium treatment in BD can significantly decrease the number of cases needed to be collected in order to achieve sufficient statistical power to detect association signals in GWAS.

Keywords: Psychiatric Genetics, Genomewide Association Study, Heterogeneity, Phenotype

Disclosure: M. Alda, Nothing to Disclose; J. Cullis, Nothing to Disclose; M. Manchia, Nothing to Disclose; R. Uher, Nothing to Disclose.

T208. Assessing Motivation in Schizophrenia in a Virtual Environment: Development of a Novel Ecologically Valid, Objective Assessment Methodology

George Foussias*, Ishraq Siddiqui, Nasteho Hasan, Krysta McDonald, Sathesan Thavabalasingam, Christina Plagiannakos, John Zawadski, Konstantine K. Zakzanis, Paul Fletcher, Albert Wong, Gary Remington

Centre for Addiction and Mental Health, Toronto, Ontario, Canada

Background: Motivational deficits have been shown to be a prominent feature of negative symptoms in schizophrenia, and confer significant functional consequences in both first-episode and chronic populations. They appear to play a direct role in predicting functional outcomes, as well as an indirect role through mediation of the relationship between cognitive impairment and functioning. However, there have been concerns around the use of subjective assessments in schizophrenia, highlighted by the discrepant findings for anhedonia in schizophrenia. In recognition of this, we sought to develop an ecologically valid objective measure of motivation using virtual reality (VR) technology coupled with a progressive ratio task, where subjects work for reward in the face of increasing effort requirements.
Methods: Stable outpatients with schizophrenia (SZ) and matched healthy controls (HC), between the ages of 18 and 55, with no other Axis I disorders or current substance abuse or dependence were recruited. All participants underwent clinical assessments for positive and negative symptom severity using the Scales for the Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS), motivational deficits with the Apathy Evaluation Scale (AES), depression with the Calgary Depression Scale for Schizophrenia (CDSS), anticipatory and consummatory pleasure using the Temporal Experience of Pleasure Scale (TEPS), cognitive function with the Brief Assessment of Cognition in Schizophrenia (BACS), and smoking status. Neurologic side effects from medications and video game experience were also evaluated. Subsequently, participants were administered our novel VR motivation task.
Results: We recruited a total of 68 subjects (34 SZ and 34 HC). Examination of performance on the VR motivation task revealed that SZ participants earned significantly lower total reward compared to HC participants ($t(66) = 2.721$, $p = .008$), and did so at a slower rate ($t(66) = 2.118$, $p = .038$), corresponding to effect sizes for the difference between groups (Cohen's d) of 0.66 and 0.51, respectively. In addition, across the entire sample, severity of motivational deficits showed significant correlations with total reward earned and rate at which subjects worked for reward. After covarying for extrapyramidal symptoms and/or video game experience, total reward earned continued to show a significant relationship with motivational deficits.
Conclusions: In recognition of the importance of motivational deficits in predicting functional outcomes in schizophrenia, and the need for objective measures to aid in both clinical evaluation and neurobiological investigations of motivational deficits, we sought to develop an objective ecologically valid measure of motivation in schizophrenia. Our results suggest that individuals with schizophrenia exhibit reduced willingness to work for reward compared to healthy controls, both in terms of the total amount of reward they earn, and the rate at which they go about earning it. In addition, this novel objective measure exhibits significant relationships with existing measures of motivational deficits in schizophrenia, although may also be assessing other aspects of motivation not evaluated by current assessment instruments. Ultimately, this methodology may provide a tool with which to rapidly assess and investigate an important aspect of motivation in individuals with schizophrenia.
Keywords: Schizophrenia Negative Symptoms Motivational Deficits Virtual Reality Effort Valuation

Disclosure: G. Foussias, **Part 1:** Dr. Foussias has served on advisory boards for Roche. He has also been involved in research sponsored by Medicure Inc., and Neurocrine Bioscience; I. Siddiqui, Nothing to Disclose; N. Hasan, Nothing to Disclose; K. McDonald, Nothing to Disclose; S. Thavabalasingam, Nothing to Disclose; C. Plagiannakos, Nothing to Disclose; J. Zawadski, Nothing to Disclose; K. Zakzanis, Nothing to Disclose; P. Fletcher, Nothing to Disclose; A. Wong, Nothing to Disclose; G. Remington, **Part 1:** Dr. Remington has received consultant fees from CanAM Bioresearch Inc., and Roche, as well as speaker's fees from Novartis. As a Principal Investigator, he has also received support from Novartis Canada, Medicure Inc., and Neurocrine Bioscience. He is also Co-Investigator in research sponsored by Pfizer Inc.

T209. Brain Region Specific Circadian Disruptions in a Mouse Model of Major Depressive Disorder

Nicole Edgar*, Andrea Gillman, Colleen A. McClung

University of Pittsburgh, Pittsburgh, Pennsylvania

Background: While the underlying brain mechanisms of major depressive disorder (MDD) are unclear, increasing evidence points towards circadian rhythm abnormalities as a component of the pathophysiology. In the brain, circadian function is controlled by the master clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, and rhythms are generated by a cycle of gene expression in individual cells, which includes a negative feedback between the CLOCK/BMAL1 proteins and the PERIOD (PER)/CRYPTOCHROME (CRY) proteins. The SCN also coordinates other subordinate oscillators in the brain, and these subordinate oscillators coordinate neuronal activity and control daily rhythms in cellular activity. In addition, recent evidence suggests that region-specific oscillations are instrumental regulators of emotional and motivational stimuli. Thus, while it is clear that individuals with MDD have circadian rhythm abnormalities, it is unclear whether the rhythmicity of circadian gene expression is selectively disrupted in brain regions associated with mood regulation and how this correlates with depressive-related phenotypes.
Methods: Here, wild type (WT) c57BL/6 mice ($N = 7$ control, 16 UCMS) were implanted with telemetry transmitters to record activity and body temperature rhythms before, during, and after exposure to four weeks of unpredictable chronic mild stress (UCMS), a paradigm that recapitulates many aspects of human MDD. A second cohort of mice carrying a fusion gene for *Period 2* and *Luciferase* (*Per2::Luc* mice) was exposed to 4 weeks of UCMS ($N = 12$ control, 11 UCMS). Mice were then sacrificed and tissue explants for 6 MDD-associated brain regions (mPFC, CeA, BLA, NAc, VTA, SCN) were assessed for circadian rhythmicity by quantifying the luminescence of luciferase (an indirect measure of *Per2* expression rhythms) over a period of seven days. Following UCMS in both cohorts, mice were tested for depression-related symptoms in the elevated plus maze (EPM), open field (OF), novelty suppressed feeding (NSF), light/dark (L/D) and forced swim tests (FST).
Results: In both cohorts, behavioral tests confirmed the UCMS paradigm induced significant anxiety and depression-related behaviors. In addition, UCMS disrupted circadian activity rhythms and this disruption persisted for several days after the UCMS paradigm was completed. In *Per2::Luc* mice, UCMS lead to a decrease in the amplitude of molecular rhythmicity in the SCN ($p < 0.05$) and surprisingly, it increased the amplitude of molecular rhythms in the mPFC ($p < 0.1$). Interestingly, region-specific changes in circadian amplitude correlate with UCMS-induced behaviors. Specifically, time in the open arm of the EPM was positively correlated with circadian amplitude in SCN and VTA, but negatively correlated with circadian amplitude in mPFC and NAc.
Conclusions: Our results indicate that the UCMS paradigm, which produces depression-related behavior, induces long-lasting alterations in circadian activity and leads to brain region-specific alterations in molecular rhythmicity. Interestingly, UCMS induces opposing changes in circadian amplitude in brain regions associated with mood and anxiety regulation, which correlate with

the severity of anxiety-related behavior. The results of this study help identify the specific role of circadian rhythm disruptions in the pathogenesis of MDD and suggest that pharmacological agents targeting circadian amplitude may have therapeutic potential.
Keywords: depression circadian chronic stress
Disclosure: N. Edgar, Nothing to Disclose; A. Gillman, Nothing to Disclose; C. McClung, **Part 1:** honorarium: Johnson & Johnson; Servier, **Part 4:** Research funding: IMHRO and Johnson & Johnson, Pfizer, Glaxo Smith Kline.

T210. Sex, Stress, and Cocaine: Role of Corticotropin Releasing Factor in Behavioral and Dopaminergic Sensitization to Cocaine

Elizabeth N. Holly, Akiko Shimamoto, Joseph F. DeBold, Klaus A. Miczek*

Tufts University, Medford, Massachusetts

Background: Brief episodes of social stress can result in cross-sensitization to cocaine in male rats. This cross-sensitization is characterized by both augmented locomotor activity and dopamine (DA) in the nucleus accumbens (NAc). Cross-sensitization can later contribute to escalated cocaine intake during a 24-hour binge. Additionally, clinical data show that females are more vulnerable than males at each phase of cocaine addiction. These sex differences have also been observed in rodents, but the role of social stress in females remains largely unexplored. Corticotropin releasing factor (CRF) has been suggested to play a key role in the development of cross-sensitization, with CRFR1 antagonism in the ventral tegmental area (VTA) prior to each social defeat episode preventing later behavioral sensitization as well as increased cocaine self-administration (Boyson et al 2011). The current study sought to extend these findings and to demonstrate that CRFR1 antagonism within the VTA can also prevent DAergic sensitization, as well as whether CRF protein levels within extra-hypothalamic regions is also altered as a result of episodic social defeat.
Methods: Male and female Long-Evans rats were subjected to four episodes, 72 hours apart, of social defeat by an aggressive resident of the same sex in the standard resident-intruder paradigm. Ten days after the last defeat episode, rats were either assessed for (1) behavioral sensitization, as determined by locomotor activity in response to acute cocaine (10 mg/kg, ip) (2) DA sensitization to acute cocaine, as measured by *in vivo* microdialysis of the NAc, (3) intravenous self-administration of cocaine (0.3 mg/kg/infusion, fixed ratio 1) in an unlimited access "binge," (4) CRF protein levels in the VTA, NAc, amygdala, and paraventricular nucleus of the hypothalamus (PVN), with samples taken by micropunch and later analyzed by an enzyme immunoassay. (5) Other rats were microinjected with the CRFR1 antagonist CP375395 prior to each social defeat, and assessed for DA sensitization to cocaine (10 mg/kg) 10 days later by *in vivo* microdialysis of the NAc.
Results: (1) Both stressed males and females showed behavioral sensitization (i.e. elevated locomotor activity) 5-10 minutes after cocaine injection, but in females the effect was both larger and more prolonged regardless of estrous cycle phase. Females in each estrous cycle phase exhibited a larger, longer lasting behavioral cross-sensitization compared to males. Rats in estrus, when circulating ovarian hormones are high, had a significantly higher locomotor activation than those in met/diestrus, when circulating ovarian hormones are low, and both groups exhibited higher locomotor activity than males. (2) While stressed males showed a significant increase in extracellular DA in the NAc compared to non-stressed males when challenged with 10 mg/kg cocaine, there was no difference in the percent baseline DA levels between stressed males and both stressed and non-stressed females. However, the augmentation in extracellular DA persisted in stressed females, while it returned to baseline within 30 minutes for all other groups. (3) Stressed males and both groups of females had similar cocaine intake during the first 24 hours of the cocaine binge, but stressed females continued cocaine taking and had a significantly longer "binge", regardless of estrous cycle phase. (4) Current experiments are verifying our hypothesis that CRF protein levels in the VTA, NAc, amygdala, and PVN of intermittently stressed animals are elevated ten days after the last defeat. (5) Consistent with our earlier studies (Boyson et al 2011), the present experiment is predicted to also confirm the hypothesis that CRFR1 antagonism within the VTA can modulate DAergic activity, preventing future DA sensitization to cocaine.
Conclusions: These data suggest that in comparison to males, socially stressed females exhibit a more robust and longer lasting behavioral cross-sensitization, as well as more dysregulated cocaine taking, possibly due to alterations in the dopaminergic response in the nucleus accumbens. Furthermore, estradiol may play a facilitatory role in both behavioral and dopaminergic sensitization, although future studies need to assess these effects more directly with ovariectomized females with and without estradiol replacement. Furthermore, preliminary data indicates CRF plays a vital role in the development of cross-sensitization to cocaine. Future studies are aimed at investigating how CRF modulates DAergic neurons in the VTA as a result of stress.
Keywords: Sex Differences, Cocaine, Sensitization, Corticotropin Releasing Factor (CRF), Dopamine
Disclosure: E. Holly, Nothing to Disclose; A. Shimamoto, Nothing to Disclose; J. DeBold, Nothing to Disclose; K. Miczek, Nothing to Disclose.

T211. Sex Differences in Fear Extinction in Men and Women Exposed to Trauma

Sabra S. Inslicht*, Thomas Metzler, Mohammed R. Milad, Scott P. Orr, Charles R. Marmar, Thomas Neylan

University of California, San Francisco VA Medical Center, San Francisco, California

Background: Epidemiological data suggests that women are twice as likely as men to develop Posttraumatic Stress Disorder (PTSD). Impairments in extinction learning and recall have been proposed as mechanisms that may impede recovery from traumatic stress exposure. This possibility has been supported by laboratory studies of fear conditioning that have found reduced extinction learning and retention associated with PTSD symptomatology. While some studies of healthy humans suggest that women are either no different or have greater extinction learning and retention than men, little attention has been placed on sex differences in fear extinction processes in men and women who have been exposed to trauma.
Methods: Fifty participants (35 men; 15 women in the early follicular phase) reporting prior trauma exposure underwent a fear conditioning procedure in which they were shown computer-generated colored circles that were paired (CS+) or unpaired (CS-) with an aversive electrical stimulus. An extinction learning task occurred 72 hours later in which participants were presented with the previously conditioned stimuli without aversive stimuli. Extinction recall was tested one week later with exposure to the previously conditioned stimuli. Skin conductance levels were assessed throughout each task. Square root differential skin conductance responses to the CS+ stimuli compared to CS- stimuli were computed and served as the dependent variable.
Results: Repeated measures ANOVA analyses revealed a significant effect of sex on differential skin conductance responses during fear conditioning, extinction learning, and extinction recall tasks. Women had greater differential conditioned skin conductance responses (CS+ trials compared to CS- trials) than did men, suggesting greater acquisition of conditioned fear in women, $F(1, 144) = 11.86$, $p < .0001$. Women also had greater differential skin conductance responses during extinction, $F(1, 489) = 4.66$, $p < .05$, and extinction recall, $F(1, 97) = 4.87$, $p < .05$, compared to men, suggesting reduced extinction learning and extinction recall in women.
Conclusions: In contrast to studies of non-trauma exposed individuals, we found enhanced acquisition of conditioned fear, reduced extinction learning, and extinction recall in follicular

phase women who have been exposed to trauma compared to men. Greater fear conditioning and impaired extinction learning and recall in women may either be a pre-existing vulnerability trait or an acquired phenomenon that emerges in a sex-dependent manner after trauma exposure. Characterizing the underlying mechanisms of these differences is needed to clarify sex-related differences in responses to trauma exposure.

Keywords: Sex differences; Fear Conditioning; Galvanic Skin Response; Posttraumatic Stress

Disclosure: S. Inslicht, Nothing to Disclose; T. Metzler, Nothing to Disclose; M. Milad, Nothing to Disclose; S. Orr, Nothing to Disclose; C. Marmar, Nothing to Disclose; T. Neylan, Nothing to Disclose.

T212. Expression Patterns of Genes Hemideleted in Williams Syndrome: Developmental and Allelic Variation Effects in Human Brain

Chao Li*, Barbara Lipska, Thomas M. Hyde, Ran Tao, Shane Kippenhan, Andrew Jaffe, Liqin Wang, Tianzhang Ye, Carlo Colantuoni, Bhaskar S. Kolachana, Venkata S. Mattay, Daniel R. Weinberger, Joel E. Kleinman, Karen F. Berman

The National Institute of Mental Health (NIMH), Bethesda, Maryland

Background: Williams syndrome (WS), a rare developmental disorder caused by hemizygous deletion of ~25 genes occupying 1.6 Mb on chromosome 7q11.23, is characterized by remarkable hypersociability, severe weakness in visuospatial construction, and relative strength in language. Molecular mechanisms by which the genetic architecture in WS conveys this unique profile of neurobehavioral changes remain unclear. To better understand the function of genes in the WS critical region, we examined expression patterns of genes in the WS locus in normal human brain across the lifespan.

Methods: We used 2-color custom spotted microarrays to measure expression of 22 genes (41 oligonucleotide probes) in the WS locus using samples from the dorsolateral prefrontal cortex (PFC) of 269 subjects with no history of psychiatric or neurological diseases, ranging in age from fetal week 14 to 85 years. All subjects were genotyped using Illumina 650K/1M Beadarrays. We also used 17 real-time quantitative PCR Taqman MGB assays to measure expression of 14 genes in the parietal cortex of 79 controls, ranging in age from 18 to78 years. Seventy-six of these subjects were included in the PFC microarray study. In a human *in vivo* structural MRI study, we assessed gray matter volume of intraparietal sulcus (IPS) as a function of genotype at rs13223593 in 279 healthy Caucasian subjects.

Results: Of 22 genes (41 probes) in the WS locus, 16 genes (24 probes) showed significant differences between average expression levels in fetal as compared with postnatal samples. Moreover, a high proportion of WS genes showed age-related changes in expression rates during early childhood and shifts in trajectories from upregulation during the fetal stage to downregulation after birth (~2.5-fold enrichment over the proportion observed throughout whole genome, $p < 0.05$), suggesting that these genes are preferentially involved in cortical development. A number of SNPs in the WS region, including rs13223593 in the *Williams Beuren syndrome chromosome region 27* gene (*WBSCR27*), showed highly significant associations with WBSCR27 expression ($p = 5.37 \times 10^{-38}$), demonstrating that allelic variation in the WS critical region affects gene expression in the human brain. We confirmed these observations in the parietal cortex (IPS), showing significant associations of the same SNPs with expression of WBSCR27 mRNA (e.g., for rs13223593, there was a significant association with WBSCR27 expression in IPS, $p = 5.74 \times 10^{-12}$). We also found that gray matter volume within the left IPS was significantly associated with variation at rs13223593 ($F = 5.9$, $p = 0.0031$) in human *in vivo* structural MRI study.

Conclusions: In this study we examined, in normal human brain, expression profiles of genes located in the 7q11.23 chromosomal region hemideleted in individuals with Williams syndrome. We found that the expression of some of these WS genes was robustly associated with SNPs and that many showed large expression differences between the fetal period and postnatal life. A disproportionately larger number of WS genes, as compared with genes in the rest of the genome, reversed the direction of their expression trajectories at the transition from the prenatal to postnatal stage of life and showed rapid changes in expression during early childhood. Together, our findings — that this chromosomal region harbors genes with sensitivity to allelic variation and with a high prevalence of early developmental changes in expression — provide a framework for understanding neurogenetic mechanisms by which some CNVs, including the WS 7q11.23 hemideletion, result in neurodevelopmental disorders while many remain silent.

Keywords: Williams syndrome (WS), postmortem human brain, gene expression

Disclosure: C. Li, Nothing to Disclose; B. Lipska, Nothing to Disclose; T. Hyde, Nothing to Disclose; R. Tao, Nothing to Disclose; S. Kippenhan, Nothing to Disclose; A. Jaffe, Nothing to Disclose; L. Wang, Nothing to Disclose; T. Ye, Nothing to Disclose; C. Colantuoni, Nothing to Disclose; B. Kolachana, Nothing to Disclose; V. Mattay, Nothing to Disclose; D. Weinberger, Nothing to Disclose; J. Kleinman, Nothing to Disclose; K. Berman, Nothing to Disclose.

T213. Using Random Forest to Generate Single Subject Treatment Outcome Predictions Based on Functional Neuroimaging

Tali Manber Ball*, Holly Ramsawh, Laura Campbell-Sills, Martin Paulus, Murray Stein

University of California, San Diego, California

Background: Anxiety disorders are highly prevalent, significantly impairing, and have profound consequences for society. However many patients respond only partially to treatment, leading to the hypothesis that individuals may not be optimally matched to the most appropriate treatment. One approach to help determine who will best respond to which treatment is to define neural substrates that predict treatment response. A variety of approaches are being used in medicine in general and psychiatry in particular to predict treatment response. Random forest classification is among the prediction methods that have proven to be the most robust, uses bootstrapping to cross-validate, and has a low tendency to over-fit, even when the number of predictors is greater than the number of subjects. However, to our knowledge this method has not been used to predict treatment outcomes in psychiatry using functional neuroimaging. Here, our primary aim was to examine the utility of random forest as a means to predict treatment outcome in anxiety disorders using functional magnetic resonance imaging (fMRI). A secondary aim was to identify brain areas contributing most to predicting treatment outcomes in two common disorders: generalized anxiety disorder (GAD) and panic disorder (PD).

Methods: 48 adults (25 with primary GAD and 23 with primary PD) completed an emotion regulation task during fMRI prior to ten weeks of cognitive behavioral therapy (CBT). The task required participants to reappraise (i.e., regulate) or maintain their emotional responses to negative images. Average activations during the reappraise and maintain conditions were extracted for each of 70 anatomically defined regions of interest, yielding 140 inputs to a random forest model. This model was used to rank the variables based on their contribution to classification accuracy using permutation importance: the top ten variables were selected for inclusion in the final model. The final model therefore

consisted of ten fMRI predictors of CBT responder or non-responder status. For comparison, a similar analysis was also conducted using self-report and demographic variables as predictors of responder status.
Results: The variables selected for inclusion in the final fMRI predictive model were right hippocampus and left uncus activation during the Maintain condition, as well as left transverse temporal gyrus, left anterior insula, right and left superior temporal gyrus, left supramarginal gyrus, left precentral gyrus, left superior frontal gyrus, and right substantia nigra activation during the Reappraisal condition. Responders demonstrated greater activation in each of these regions than did non-responders. The final model with these ten variables yielded an overall accuracy of 79.17%, with sensitivity of 0.86 and specificity of 0.68. The positive likelihood ratio of 2.73 (95% confidence interval: 1.39, 5.38) and negative likelihood ratio of 0.20 (95% confidence interval: 0.08, 0.53) were statistically significantly different as evidenced by non-overlapping confidence intervals. In contrast, the random forest model using self-report and demographic variables yielded poorer overall accuracy (68.75%), sensitivity (0.79), and specificity (0.53).
Conclusions: To our knowledge, this is the first study to use random forests to predict treatment outcome based on functional neuroimaging in anxiety disorders. The regions selected by the model, particularly the anterior insula and superior frontal gyrus, suggest that greater activation in key cortico-limbic circuitry may specifically predict CBT outcomes in GAD and PD, although these results should be confirmed in an independent sample. Taken together, random forest models built with fMRI may be able to provide single subject predictions with adequate accuracy, sensitivity, and specificity. Moreover, fMRI variables outperformed the model comprised of self-report and demographic variables, suggesting that fMRI may have a role in predicting important mental health outcomes and thereby personalizing treatment.
Keywords: Anxiety disorders, fMRI, treatment outcome, prediction, emotion regulation
Disclosure: T. Manber Ball: Nothing to Disclose; H. Ramsawh: Nothing to Disclose; L. Campbell-Sills: Nothing to Disclose; M. Paulus: Nothing to Disclose; M. Stein: **Part 2**: Dr. Stein is a consultant for Care Management Technologies, and is paid for his editorial work at Up To Date, Inc. (Co-Editor-in-Chief, Psychiatry) and Depression and Anxiety, Wiley Press (Deputy Editor).

T214. Frontostriatial Activation Abnormalities during Sustained Attention and Inhibitory Control Among Patients with Late Life Depression

Sara L. Weisenbach*, Bridget Cornett, Erich Avery, Brennan Haase, Jon-Kar Zubieta, Scott Langenecker

University of Michigan Medical School, Ann Arbor, Michigan

Background: The depression-executive dysfunction syndrome of late life (DEDS) posits that frontostriatal dysfunction is the main predisposing factor to depression in a subgroup of older adults with late life depression (LLD). Support for this syndrome comes from studies finding executive functioning deficits among patients with LLD relative to their non-depressed peers (Butters et al., 2004). Structural imaging studies also demonstrate white matter pathology in subcortical structures and their frontal projections among some patients with LLD, and functional studies have shown abnormal activation of prefrontal and striatal regions during a cognitive challenge (Aizenstein et al., 2006, 2009), and abnormal functional connectivity of bilateral frontal regions during the resting state (Yuan et al., 2008) among LLD patients. The current study sought to extend support for this syndrome by a) investigating sustained attention and inhibitory control performance among a relatively large sample of LLD patients relative to same-age peers; b) examining disruption to frontostriatal pathways during fMRI challenge among a smaller sample of patients; and c) relating activation to performance.
Methods: In Study 1 (neuropsychological study), participants included 48 older adults with LLD (31 female, M age = 70.90, SD = 9.54), as assessed with the Structured Clinical Interview for DSM-IV (First et al., 2002) and 60 never-depressed controls (HC; 35 female, M age = 65.98, SD = 9.11). The LLD group was significantly younger than the HC group ($p < .01$), and thus age was used as a covariate in all analyses. In Study 2 (neuroimaging study with fMRI), participants included 11 LLD (8 female, M age = 66.73, SD = 6.71) and 13 HC (5 female, M age = 69.00, SD = 5.20). Age was used as a covariate in all functional analyses, though it was not significantly different between the two groups ($p > .05$). Both groups were free of major medical or neurological conditions, including dementia (by history and MMSE > 24), as well as free of current substance abuse. Patients with MDD could have no comorbid diagnoses besides anxiety disorder(s). In Study 1, participants completed the Parametric Go-No-Go Task (PGNG), which entails three levels of increasing difficulty that require sustained attention and inhibitory control. Behavioral data were analyzed with analyses of covariance. In Study 2, participants underwent the PGNG task during fMRI using a 3T GE Signa scanner for whole brain scanning. Functional imaging data were processed and analyzed using MATLAB and SPM2 (first-level analyses) and SPM8 (second level analyses). A two-sample *t*-test was conducted. The main contrast of interest for the purpose of this study was activation during level one of the PGNG, performed as the distractor task for a semantic memory measure. Second-level analyses were performed using a mask encompassing the superior, middle, medial, and inferior frontal gyri, anterior cingulate, and caudate, created using the Wake Forest PickAtlas. A corrected $p < .05$, cluster minimum of 80 mm3 thresholds was used for all analyses.
Results: In Study 1, the LLD group were less accurate in their performance on Level 1 ($F(1, 106) = 6.47$, $p = .01$), but not Levels 2 or 3 of the PGNG ($ps > .05$). Reaction times for the two groups were similar across all three levels ($ps > .05$). In Study 2, the LLD and HC groups demonstrated distinct patterns of activation, such that the LLD group demonstrated activation in more lateral regions of the prefrontal cortex, while activation in the HC group was more medial. The LLD group had a greater number of regions activated relative to the HC group, including multiple regions of prefrontal cortex and caudate. Performance was not significantly correlated with any of the regions that were differentially activated between the LLD and HC groups, with the exception of one region of the superior frontal gyrus, which was negatively correlated with commission errors ($r = -.42$, $p < .05$).
Conclusions: Patients with LLD are less accurate and demonstrate differential patterns of activation (that is more lateralized) on a measure of sustained attention and inhibitory control relative to their non-depressed peers. Activation was, by and large, not related to performance. These findings provide further support for the DEDS and suggest that patients with LLD may be less efficient than healthy older adults on tasks requiring sustained attention and inhibitory control. Future research in a larger sample might consider whether frontoexecutive dysfunction is predictive of cognitive decline and course of illness in patients with LLD.
Keywords: late life depression, executive functioning, fMRI
Disclosure: S. Weisenbach, Nothing to Disclose; B. Cornett, Nothing to Disclose; E. Avery, Nothing to Disclose; B. Haase, Nothing to Disclose; J. Zubieta, **Part 1:** Eli Lily-Speakers Bureau, **Part 2:** Eli Lily-Speakers Bureau, **Part 3:** Eli Lily-Speakers Bureau; S. Langenecker, Nothing to Disclose.