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M2. Elevations of Brain Kynurenic Acid in Prenatal Rats Result in Long-lasting Impairments in Cortical Development and Cognitive Flexibility: Implications for Schizophrenia

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Background: Schizophrenia (SZ) is a debilitating psychiatric disorder that presents with cognitive deficits in thought processing, attention and working memory. Though cognitive deficits are considered core symptoms and are predictive of functional outcome, they remain largely unresolved by current drug and behavioral interventions. Thus, continued study of validated animal models may provide a platform for revealing more efficacious cognition-enhancing medications. Elevated kynurenic acid (KYNA) levels in the brain of patients with SZ may contribute to these cognitive impairments through KYNA's negative allosteric modulation of α7 nicotinic acetylcholine receptors (α7*nAChRs) and subsequent reductions in extracellular cortical ACh and glutamate levels. This hypothesis has prompted the use of experimental elevations in brain KYNA, at different stages of the life span, as a model of SZ. We have reported that administration of KYNA's bioprecursor (kynurenine) from gestational day (GD) 15 through weaning produces deficits in hippocampal- and prefrontal-mediated tasks when offspring are tested as adults. In the present experiments, we further delineated the sensitive period by elevating brain KYNA in fetuses during the last prenatal week (GD15-22). Given the role of α7nAChR activity in the development of excitatory synapses and ultimately in the mediation of cognitive flexibility via prefrontal cholinergic and glutamatergic transmission, we determined the impact of prenatal elevations of KYNA on several indices of cortical excitability, including the density of dendritic spines on cortical pyramidal neurons (layers II/III), the expression of mGluR2 mRNA, and evoked glutamate release in prefrontal cortex (PFC).
Methods: Subjects: KYNA levels wereelevated chronically from GD 15 through GD22, by adding KYNA precursorkynurenine (100 mg/day) daily to reconstituted powdered rat chow fed topregnant Wistar rats (EKyn). In thecontrol condition, mothers were fed unadulterated reconstituted powdered ratchow (ECon) for the same time period. Post parturition, dry rat chow pellets were fed to dams and offspringuntil the latter were tested for neurochemical or behavioral outcomes beginningat PD56. **KYNA levels:** Serumlevels of kynurenine were measured in litter-matched maternal and pup samples fromGD21 (EKyn = 9 pups, from 3 litters: ECon = 12 pups, 4 litters) and PD2 (EKyn = 12pups, 4 litters: ECon = 18 pups, 6 litters), as well as adult offspring on dayPD56 (EKyn = 5 rats, 3 litters: ECon = 5 rats, 3 litters). To determine brain KYNA levels at those sametime points, forebrain or PFC tissue homogenates were analyzed from those sameanimals. **Cortical excitability:** Densities of apical and basal dendritic spines (expressedas spines per 10 μm) werecalculated using Golgi-impregnated pyramidal neurons from the prelimbic/infralimbiccortex (layer II/III; EKyn = 6 pups, 4 litters; ECon = 7 pups, 4 litters). 4–5 neurons per animal, and 3–5 segments per neuron were analyzed. **RTqPCR:** Expressionlevels of mGluR2 mRNA were determined in brain homogenates at GD21 (EKyn = 6pups, 3 litters: ECon = 8 pups, 4 litters), PD2 (EKyn = 8 pups, 6 litters: ECon = 12pups, 6 litters), and PD56 (EKyn = 4 rats, 2 litters: ECon = 3 rats, 1 litter). **Evokedglutamate release:** The mesolimbic stimulation of prefrontal glutamatewas quantified using a glutamate-sensitive amperometric microelectrode arrayfollowing intra-nucleus accumbens infusions of NMDA (0.05–0.30 μg/0.5μL)(EKyn = 5 pups, 4 litters; ECon = 7 pups, 5 litters). **Set Shifting Behavior:** Cognitiveflexibility was assessed between PD56-80 using an attentional set-shifting task(ASST) (EKyn = 8 pups, 5 litters; ECon = 7 pups, 4 litters).
Results: KYNA levels: Compared to controls, serum kynurenine was increased in EKyn dams and offspring on GD21 (dams = 2223%, fetuses = 692%) but not on PD2. EKyn rats had elevated brain KYNA levels, relative to ECon, on GD21 (400%) and PD56 (150%). **Cortical excitability:** Relative to ECon, EKyn rats showed reductions in apical (by 11%) and basal (by 14%) dendritic spine density of pyramidal neurons in layer II/III of the prelimbic/infralimbic cortex as well as reduced expression of mRNA for mGluR2 in frontal cortex at GD21 (by 28%) and PD56 (by 27%). **Evoked glutamate release:** The mesolimbic activation of prefrontal glutamate release following intra-accumbens infusion of NMDA seen in ECon rats (3.58 ± 0.40 μM increase after 0.15 μg NMDA) was nearly eliminated (0.43 ± 0.22 μM) in Ekyn rats. **Set Shifting Behavior:** In adulthood, EKyn rats exhibited deficits in the ASST at the first reversal (twice as many trials to criteria) and extra-dimensional shift (58% more trials to criteria) stages.
Conclusions: Consistent with the role of α7nAChRs on neuronal development, prenatal elevation of the negative modulator KYNA in the last week of gestation produces long lasting neuronal changes that are associated with deficits in cortical excitability and cognition as adults. These changes include reductions in spine density, expression of mGluR2 mRNA, evoked glutamate release in PFC, and also reduced cognitive flexibility. As each of these changes has been described as part of the pathology accompanying SZ, these results further validate prenatally elevated KYNA levels as a valuable animal model of the disease.
Keywords: kynurenic acid, development, glutamate, cognition, schizophrenia
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R. Schwarcz, **Part 1:** Research support from Mitsubishi-Tanabe; Bristol-Myers-Squibb (ended 2012) and Lundbeck (will start 2013).

M3. Evidence for Both an Alpha7 Nicotinic and a Glycine B Receptor Mediation of Working Memory in the Rat

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Background: Cognitive deficits (attention, working memory, and cognitive flexibility) are considered a core symptom cluster in schizophrenia (SZ); predictive of functional outcome yet not alleviated by current drug and behavioral interventions. Thus, there is a need for further studies on animal models to reveal more efficacious pharmacotherapies. A significant contributor to cognitive impairments seen in SZ may be the elevated levels of kynurenic acid (KYNA), observed in the brains of patients with SZ. KYNA is an endogenous, astrocyte-derived metabolite that negatively modulates α7 nicotinic acetylcholine receptors (α7nAChRs) at physiological concentrations and, at higher concentrations, blocks the glycine$_B$ site of the NMDA receptor. We have reported that acute administration of KYNA's bioprecursor L-kynurenine (KYN; 100 mg/kg) in intact adult rats increases extracellular KYNA (~1,500%), decreases extracellular glutamate (GLU) levels (~30%) in the prefrontal cortex (PFC), and behaviorally results in an impairment of the prefrontally-mediated attentional set shifting task. We investigated three issues: (1) whether the impairing effects of acute KYNA elevations can be generalized to another PFC-mediated task, the Delay Non-Match to Position (DNMTP) working memory task; (2) whether KYNA-induced working memory deficits would be alleviated by the administration of the α7nAChR-positive modulator galantamine (GAL). Our previous results indicated that KYN's reduction of GLU release is restored to basal levels following administration of GAL, and that GAL normalizes performance in a set shifting task in a different KYNA-based animal model of SZ; and (3) the relative roles of α7nAChRs vs NMDA receptors in performance in the DNMTP task.To this end, we determined, in a separate group of intact animals, the effects of an acute administration of 4-chlorokynurenine (4-ClKYN), a bioprecursor of the selective glycine$_B$ antagonist 7-chlorokynurenic acid (7-ClKYNA),. We predicted working memory deficits following 4-ClKYN but, in contrast to the effects of KYN, we expected no restoration of performance following co-administration of GAL.
Methods: Acquisition training in the Delayed Non-Match to Position (DNMTP) task began, in 2 groups of adult male Wistar rats, at postnatal day (PD) 56. After acquisition and baseline performance was established at each of the 3 delay periods (5, 10, and 15 s), rats received a series of drug challenges. Rats in the first group ($N = 8$) received an acute injection (i.p.) of 0 (vehicle), 25 or 100 mg/kg KYN (dose order randomized) 50 min prior to the session, with a minimum of 48 h between test days to assure complete return to basal performance levels. After completing the KYN dose response curve, animals were tested again 50 min following injection of KYN (100 mg/kg) + GAL (3 mg/kg). Following the same protocol, a second group of rats ($N = 8$) received 0 (vehicle), 25 or 100 mg/kg 4-ClKYN, or 4-ClKYN (100 mg/kg) + GAL (3 mg/kg).
Results: In both groups of rats, performance under the control condition was delay-dependent. In the KYN-treated group, accuracy was 95, 87, and 82% at 5, 10, and 15 s, respectively. Elevation of KYNA via acute administration of KYN resulted in significant deficits in performance and, as expected, the detrimental effects were largest for the higher dose and longest delays. Compared to vehicle treatment, 25 mg/kg KYN significantly reduced accuracy (by 12%) only at the longest delay (15 s), while 100 mg/kg significantly reduced accuracy at 5 s (by 11%), 10 s (by 14%), and during the 15 s delay (by 33%; dropping to chance levels). Compared to vehicle, acute KYN (both 25 and 100 mg/kg) produced a four-fold increase (from ~9 to ~40) in sample phase omissions during the first 15 min of the task. The detrimental effects of 4-ClKYN were more severe than those caused by KYN. Vehicle treatment accuracy was 96%, 87%, and 77% at 5, 10, and 15 s. 25 mg/kg 4-ClKYN reduced accuracy (by 33%) at the 15 s delay, while 100 mg/kg 4-ClKYN significantly reduced accuracy overall (by 60%) as well as at all delays, well below chance performance, 5 s (by 54%), 10 s (by 60%), and 15 s delays (by 70%). There was no significant increase in omissions following acute administration of 4-ClKYN. Notably, the deficits following acute administration of 100 mg/kg KYN were fully prevented by co-administration of GAL. In contrast, the deficits following 100 mg/kg 4-ClKYNA were unaffected by treatment with GAL.
Conclusions: Collectively, these findings suggest a role for both α7nAChRs and NMDA receptors in the mediation of working memory. Acute elevation of KYNA in adult rats results in significantly reduced, delay-dependent performance in the DNMTP task. This deficit appears to result from KYNA's negative allosteric modulation of α7nAChRs, as performance accuracy was normalized by GAL. Acute elevation of the glycine$_B$ antagonist 7-ClKYNA resulted in even more severe deficits in performance, and these impairments were not reversed by co-administration of GAL. Considering evidence for impairments in both nicotinic and glutamatergic transmission in SZ, these data in animals provide support for the continued focus on the α7nAChR and NMDA receptor as targets for cognition enhancement in SZ.
Keywords: kynurenic acid, development, glutamate, cognition, schizophrenia
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M4. Attenuation of Metabolic Consequences from Atypical Antipsychotic Use in Schizophrenia: Folate Supplementation and the Role of Pharmacogenomics

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Background: Metabolic syndrome may be related to dietary folate, its pharmacogenetically regulated metabolism, and

atypical antipsychotic (AAP) exposure. We examined how folate supplementation would affect metabolic measures and endothelial functioning (RHI) in AAP treated schizophrenia subjects meeting NCEP-ATP-III metabolic syndrome criteria.
Methods: Subjects were given 5 mg/day open label folate for 3 months. Baseline and 3 month measurements included RHI, BMI, fasting metabolic laboratory measures, C-reactive protein, homocysteine, IL-6, and leptin. DNA was gentoyped for the methylenetetrahydrofolate reductase (*MTHFR*) 677C/T and catechol-O-methyltransferase (*COMT*) 158 Val/Met variants.
Results: Thirty-five subjects with a mean age of 50 ± 9 years and 70% Caucasian. After 3 months supplementation, RHI improved by 20% ($p = 0.02$), mean homocysteine decreased 14% ($p = 0.006$), and IL-6 decreased 13% ($p = 0.09$). Subjects exercised 15% less during the study ($p = 0.05$). At baseline 61% met endothelial dysfunction criteria (RHI < 1.67), which decreased to 27% ($p = 0.0006$) at endpoint. The *MTHFR* 677C/C + *COMT* 158Met/Met subjects had a 44% RHI improvement versus 10% improvement for *MTHFR* 677T/*COMT* Val allele carriers ($p = 0.06$). The *MTHFR* 677C/C + *COMT* 158Met/Met group also showed significant reduction in those meeting endothelial dysfunction (83% baseline and 16% endpoint), compared to the *MTHFR* T + COMT Val allele carriers (54% baseline and 31% endpoint[$p = 0.001$]).
Conclusions: Folate may reduce AAP-associated metabolic risks and we report significant reductions in the number of subjects meeting endothelial dysfunction. This is remarkable given that ALL subjects met metabolic syndrome criteria. This may prove as a useful avenue to reducing CVD risk. Those with the MTHFR T or COMT Met alleles may not benefit from folate, but this needs further follow up.
Keywords: folate, MTHFR, schizophrenia, metabolic syndrome
Disclosures: V. Ellingrod, Nothing to Disclose; T. Grove, Nothing to Disclose; S. Taylor, Nothing to Disclose; K. Burghardt, Nothing to Disclose.

M5. Weight Gain Independent, Centrally-mediated Effects of Olanzapine on Glucose Metabolism

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Background: The atypical antipsychotics (AAPs) have been associated with an increased risk of metabolic abnormalities. However, the mechanism of antipsychotic-induced metabolic side effects, in particular glucose dysregulation remains unclear. In this regard, evidence from preclinical models supports pronounced effects on insulin sensitivity and secretion occurring independently of adiposity, following acute dosing of specific AAP agents. However, this model of systemic drug administration is unable to differentiate peripheral from central effects on glucose homeostasis. Given evidence suggesting a critical role for the hypothalamus in direct control of energy and glucose metabolism, we set out to clarify central mechanisms of olanzapine (OLA)-induced glucose dysregulation.
Methods: Healthy Sprague-Dawley rats were treated with a single 75 μg intracerebroventricular (ICV) dose of OLA or vehicle, and tested using hyperinsulinemic-euglycemic and hyperglycemic clamp procedures which are considered the gold-standard to assess insulin sensitivity and pancreatic β-cell response, respectively. Dosing of OLA was established based on inhibition of amphetamine-induced locomotion, a validated model of antipsychotic efficacy. Data was analyzed using mixed-models repeated-measures analyses, with significance accepted at $p < 0.05$.
Results: Analogous to our previous findings demonstrating that a single peripheral dose of clozapine and OLA is able to induce a deficit in β-cell function, a single ICV dose of OLA followed by the hyperglycemic clamp procedure resulted in decreased insulin ($p = 0.0041$) and c-peptide response ($p = 0.0039$) to glucose challenge as compared to vehicle-treated animals. This was also mirrored by a significant decrease in the steady-state glucose infusion rate required to maintain hyperglycemia ($p = 0.002$). In contrast to the single dosing peripheral paradigm, there was no effect of ICV OLA on insulin sensitivity, with tracer studies failing to show an effect on hepatic glucose production or peripheral glucose uptake.
Conclusions: We show that a single centrally administered dose of OLA impairs β-cell secretory function, suggesting that the central nervous system may be an important site in mediating drug-related effects on insulin response. The lack of a central OLA effect on insulin sensitivity might suggest that peripheral mechanisms play a more prominent role in the perturbations seen with systemic administration, likely through direct effects on tissues implicated in glucose metabolism.
Keywords: atypical antipsychotics, intracerebroventricular, glucose dysregulation, diabetes
Disclosures: M. Hahn, Nothing to Disclose; A. Chintoh, Nothing to Disclose; G. Remington, **Part 1:** Paid consultant or speaker for Novartis, Laboratorios Farmacéuticos Rovi, Synchroneuron, and Roche., **Part 4:** Research support from the Canadian Diabetes Association, the Canadian Institutes of Health Research, Medicure, Neurocrine Biosciences, Novartis Canada, Research Hospital Fund–Canada Foundation for Innovation, and the Schizophrenia Society of Ontario; C. Teo, Nothing to Disclose; S. Mann, Nothing to Disclose; P. Fletcher, Nothing to Disclose; J. Nobrega, Nothing to Disclose; A. Giacca, Nothing to Disclose.

M6. Disturbances of Tryptophan Metabolism and Risk of Depression in Hcv Patients Treated with Ifn-Alpha

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Background: Serotonin deficiency is associated with majordepressive disorder. It was suggested that serotonin deficiency is caused bythe shunt of tryptophan (TRP)

metabolism from biosynthesis of serotonin toformation of kynurenine (KYN). The rate-limiting enzyme of TRP—KYNmetabolism, indoleamine 2,3-dioxygenase (IDO), is transcriptionally induced bypro-inflammatory factors, e.g., interferon-gamma (IFNG). IFNG production is encodedby polymorphic IFNG (+ 874) T/A. We reported that presence of high producerallele (T) of this gene increased the risk of depression as a side-effect ofIFN-alpha treatment of hepatitis C virus (HCV) patients. Therefore, we expected-positive correlation between activity of IDO (and TRP—KYN metabolism) andrisk of depression in HCV patients treated with IFN-alpha. Our aim was evaluation of serum levels of TRP, KYN and KYN derivative, kynurenic acid (KYNA) in HCV patients who developed and who did notdevelop depression during IFN-alpha treatment.
Methods: Kynurenines were detected by HPLC-fluorometricmethod in serum samples of 80 HCV patients awaiting treatment. Depression wasassessed by SCID-IV. Study was approved by Tufts Medical Center IRB.
Results: There was no difference in KYN, KYNA levels and KYN/TRPratio (KTR) between patients who developed ($n = 43$) and who did not develop ($n = 37$)depression during IFN-alpha treatment. TRP concentrations were higher inpatients who developed depression ($p < 0.05$, Kruscal-Wallis test). Odds ofdevelopment of depression increased as TRP levels elevated from 33% (TRP levels < 12000 pmol/ml) to 68% (TRP levels > 16000 pmol/ml, $p < 0.05$).
Conclusions: Obtained data did not confirm our working hypothesis of up-regulation of TRP—KYN metabolism as a risk factor for depression in HCV patients treated with IFN-alpha. The unexpected finding of association of elevated serum TRP concentrations with the risk of depression (without changes of TRP—KYN metabolism) suggest the deficiency of conversion of TRP into serotonin as depression risk factor in HCV. Polymorphism of the rate limiting enzyme of TRP—serotonin pathway, tryptophan hydroxylase (Tph), is associated with depression in animal and human studies. Our data warrant the further studies of Tph polymorphism as a risk factor for depression associated with IFN-alpha treatment of HCV patients.
Keywords: tryptophan, kynurenine, depression, interferons, hepatitis C
Disclosures: G. Oxenkrug, Nothing to Disclose; W. Turski, Nothing to Disclose; W. Zgrajka, Nothing to Disclose; J. Weinstock, Nothing to Disclose; P. Summergrad, Nothing to Disclose.

M7. Sensitive Biomarkers of Metabolic Risk in Children Treated with Antipsychotics

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Background: Individuals with psychiatric illnesses who are chronically treated with antipsychotic medications are known to be at increased risk for developing diabetes and cardiovascular disease. However, whether this increased risk is primarily due to weight gain and increased adiposity, psychiatric diagnosis or antipsychotic treatment status is unknown. It is critical to identify those individuals at greatest risk for disease in order to accurately target prevention and treatment approaches. The identification of proximate, noninvasive biomarkers of metabolic risk for use as surrogate markers can address this problem. Carotid artery intima media thickness (CIMT) is a known indicator of risk for developing cardiovascular disease, and changes in CIMT are positively correlated with metabolic syndrome criteria in otherwise healthy youth. Magnetic Resonance Spectroscopy (1 H MRS) measuring hepatocyte triglyceride content (HTGC) is a surrogate measure of steatohepatitis, the most common liver abnormality found in children. The present study explored the relationship between adiposity, CIMT and HTGC in a cohort of antipsychotic-treated youth and Body Mass Index percentile (BMI%ile)-matched healthy controls. We hypothesized that level of adiposity, irrespective of antipsychotic treatment status, would be the primary predictor of metabolic risk as measured by CIMT and HTGC.
Methods: Participants were antipsychotic-treated youth and healthy controls ages 6–19, matched between groups across a range of BMI %ile spanning normal, overweight and obese. Primary outcome measures included CIMT, measured with 9-MHz B-mode ultrasonography and HTGC, measured with 1 H MRS of the liver. Body composition was measured via Dual Energy X-Ray Absorptiometry (DEXA). Additional plasma measures included fasting glucose, insulin and lipids, as well as fibrinogen, high-sensitivity C-reactive protein (hs-CRP), 25-hydroxyvitamin D and liver enzymes. Analysis of Covariance (ANCOVA) and multiple stepwise regression analyses were used to identify separate best-fit models for the prediction of CIMT and HTGC values, testing the predictive values of individual and combinations of conventional variables. The dependent variables of interest were CIMT and HTGC; the primary covariate was DEXA total % fat. All analyses were performed using SPSS.
Results: A total of 43 children, mean age 11.5 (SD 2.9, SE = 0.4) years participated in the study (antipsychotic treated $n = 24$, healthy controls $n = 19$). Groups were closely matched on age, gender, waist circumference and BMI%ile. Ten patients were receiving aripiprazole at a mean daily dose of 7.6 mg (SD = 5.6, SE = 1.8), 7 were receiving olanzapine at a mean daily dose of 3.9 mg (SD = 2.0, SE = 0.7), 6 were receiving risperidone at a mean daily dose of 1.5 mg (SD = 2.2, SE = 0.9), and 1 was receiving quetiapine at a mean daily dose of 100 mg. There were no significant differences between BMI%ile matched patients and controls on CIMT ($F[1,40] = 1.95$, $p = 0.17$) or HGTC ($F[1,42] = 1.46$, $p = 0.23$). In addition, no group differences were observed on BMI%ile ($F[1,42] = 1.31$, $p = 0.26$), DEXA percent fat ($F[1,42] = 0.67$, $p = 0.42$) fasting glucose ($F[1,42] = 0.20$, $p = 0.65$) or fasting insulin ($F[1,42] = 1.55$, $p = 0.22$). In the overall sample, DEXA total % fat explained the majority of the variance in both CIMT (34%, $F[1,40] = 20.08$, $p \leqslant 0.0001$) and HTGC (30%, $F[1,42] = 17.58$, $p \leqslant 0.0001$). Further, BMI%ile accounted for 30.4% of the variance in CIMT ($F[1,40] = 17.02$, $p \leqslant 0.0001$) and 15.2% of the variance in HTGC ($F[1,42] = 7.35$, $p = 0.01$). Other plasma variables (eg fasting glucose, lipids, insulin, inflammatory markers and HOMA-IR) contributed to variance in both HGTC and CIMT, but to a lesser degree.
Conclusions: This is the first study we know of to examine sensitive indicators of metabolic risk like CIMT and HTGC

in youth treated with antipsychotic agents. The results of this study, conducted in both treated and untreated youth, indicate that adiposity measured either by DEXA or BMI%ile was a consistent predictor of metabolic risk measured either by CIMT or HTGC. The strength of this relationship did not differ when comparing treated psychiatric patients versus untreated healthy controls, indicating the importance of adiposity as a general predictor of metabolic risk in youth, regardless of antipsychotic treatment status. Plasma markers, such as fasting glucose, lipids and insulin, had less of a predictive effect on CIMT and HTGC. These results suggest that screening and monitoring efforts in this population may be most effectively focused on clinically available surrogate measures of body composition and adiposity, such as BMI%ile.

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Keywords: child psychiatry, antipsychotic, obesity

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M8. Increased Rate of Chiari I Malformation in Children of Depressed Mothers Treated with Selective Serotonin Reuptake Inhibitors during Pregnancy

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Background: Recent estimates suggest over 10% of pregnant women fill prescriptions for Selective Serotonin Reuptake Inhibitors (SSRIs). Research on prenatal SSRI exposure effects on child health has yielded conflicting results, and is scarce regarding brain development. The objective of the current study was to determine whether there is a statistically significant increase in Chiari I malformations (CIM) in children with prenatal exposure to selective serotonin reuptake inhibitors (SSRI). CIM is a condition in which the cerebellar tonsils extend below the foramen magnum, increasing risk for a variety of neurological phenomena including headaches, ocular and otoneurological disturbances, lower cranial nerve signs, hydrocephalus, and spinal cord syrinx.

Methods: In this retrospective cohort study,33 children whose mothers had received a diagnosis of depression and took SSRIs during pregnancy were matched to 66 unexposed controls whose mothers did not have a diagnosis of depression. In addition, 30 children whose mothers had received a diagnosis of depression, but did not receive antidepressants during pregnancy, were matched to 60 unexposed controls whose mothers did not have a diagnosis of depression. The main outcome measure was presence/absence of CIM on MRI scans at 1 and/or 2 years of age. Scans were reviewed by 2 independent neuroradiologists, blind to exposure status.

Results: SSRI exposed children were significantly more likely to be classified as CIM than controls (18% versus 2%). Duration of exposure increased risk. Children of mothers who had received a diagnosis of depression, but did not receive antidepressants during pregnancy, did not differ from controls in occurrence of CIM (7 *vs* 5%).

Conclusions: This study found a significant increase of CIM in children with prenatal SSRI exposure. As CIM was not elevated in children of mothers with a history of depression, but no antidepressant treatment during pregnancy, we feel we can rule out shared genetic risk for CIM and depression. Additional research is needed to clarify whether SSRIs directly impact risk for CIM or whether this relationship is mediated by severity of depression during pregnancy.

Keywords: SSRI, depression, pregnancy

Disclosures: R. Knickmeyer, **Part 1:** Dr. Knickmeyer is a collaborator on 2 investigator-initiated grants from Pfizer (no salary support is included)., **Part 4:** Dr. Knickmeyer is a collaborator on 2 investigator-initiated grants from Pfizer (no salary support is included).; S. Meltzer-Brody, **Part 1:** Dr. Meltzer-Brody received research grant funding from Astra Zeneca (investigator initiated study), **Part 4:** Dr. Meltzer-Brody received research grant funding from Astra Zeneca (investigator initiated study); S. Woolson, Nothing to Disclose; R. Hamer, **Part 1:** Dr. Hamer has served on an advisory board, or consulted on a clinical trial, or served on a DSMB, for Abbott, Allergan, Alkermes, Cenerx, Columbia University, Endo, Lilly, Novartis, Pfizer, Roche, Wyeth, and has served as an expert witness in cases involving Forest, Lundbeck, Sun, Caraco, Teva, Barr, Mylan, Eurand, Cephalon, Anesta, and Marial. ; K. Smith, Nothing to Disclose; K. Lury, Nothing to Disclose; J. Gilmore, Nothing to Disclose.

M9. Olanzapine and Diet Affect CNS and Peripheral Metabolic Outcomes in a Non-human Primate

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Background: Clinical and animal data suggest that atypical antipsychotics such as olanzapine (OLZ) induce significant metabolic changes that are serious side effects of their primary use. Since controlled human studies are problematic and rodent data may be poorly translatable, we sought a macaque model of OLZ-induced metabolic disease. Normal monkey chow contains significantly lower calories from sugar and fat compared to a western style diet (WSD). Therefore, we examined metabolic endpoints in the presence and absence of OLZ with monkey chow or WSD.

Methods: A female Japanese macaque was administered OLZ (5 mg/kg/day) for 6 months, with dietary changes at 2-month intervals as follows: OLZ + restricted chow, OLZ + unrestricted chow, OLZ + WSD, and placebo + WSD. Weight was accessed weekly, with glucose tolerance tests (GTT) and Dexascans performed at baseline and every 2 months. To evaluate adipose-specific effects, visceral (V) and subcutaneous (SC) adipose tissue biopsies were obtained at baseline and after OLZ + unrestricted chow and OLZ + WSD to evaluate adipocyte size, lipolysis and insulin-stimulated fatty acid uptake. A separate trial was conducted on 2 monkeys with 5 days of OLZ- or no-treatment followed by RT-PCR on rostral and medial basal hypothalamus (MBH).
Results: Weight increased on OLZ + restricted chow and stabilized on OLZ + unrestricted chow. OLZ + WSD did not significantly change the plateau in 2 months. Weight declined upon withdrawal of OLZ with continued WSD. Body fat increased from 14% at baseline to 22%, 30%, 28% and 19% at 2, 4, 6 and 8 mo, respectively, indicating that body fat was elevated on OLZ regardless of diet and declined upon OLZ removal. Fasting glucose levels were normal; and glucose tolerance and the insulin response during GTT were normal with OLZ + restricted chow or OLZ + unrestricted chow. Addition of WSD with OLZ impaired glucose tolerance during GTT. Insulin remained in the normal range, but first phase insulin secretion was reduced. Hence, insulin did not respond to elevated glucose during GTT. After removal of OLZ but continued WSD, glucose clearance returned to normal. However, this was associated with hyperinsulinemia, perhaps triggered by early insulin resistance. Adipocyte diameter was increased in V and SQ fat by OLZ + chow and OLZ + WSD ($p < 0.01$, 2-way ANOVA), but OLZ + WSD was not different from OLZ + chow. Isoproterenol-stimulated lipolysis was present in V and SQ fat. Lipolysis was similar between baseline and OLZ + chow, but it was significantly reduced by addition of WSD (ANOVA $p < 0.0001$; posthoc $p < 0.05$). Insulin increased FFA uptake at baseline. However, insulin-induced FFA uptake was blunted with OLZ administration + chow or + WSD in both V and SC fat (posthoc $p < 0.05$), suggesting the early development of adipose insulin resistance. There was an increase in expression of AgRP and a decrease in expression of CART & ghrelin in MBH and rostral hypothalamus compared to untreated control tissue. 5HT2C mRNA increased and POMC mRNA decreased in the MBH with OLZ treatment. There was no apparent change in MCR4 in either region.
Conclusions: We conclude that OLZ acts on peripheral tissues as well as in the CNS; that changes in hypothalamic gene expression precede increased fat accumulation; that adipose tissue exhibits insulin resistance prior to alterations in GTT/ITT; that addition of WSD to OLZ precipitates impaired glucose tolerance without an obvious insulin response; and that removal of OLZ and continued WSD resulted in normalized glucose tolerance and elevated insulin. These data suggest OLZ rapidly changes hypothalamic gene expression; decreases insulin sensitivity in adipose tissue, and may suppress insulin with high fat diet. These data suggest complex and early responses to OLZ that may be exacerbated by WSD. Further study is needed with more animals.
Keywords: atypical antipsychotics, olanzapine; weight, body fat, glucose, insulin resistance, hypothalamus

Disclosures: C. Bethea, Nothing to Disclose; O. Varlamov, Nothing to Disclose; P. Kievit, Nothing to Disclose; A. Reddy, Nothing to Disclose; C. Roberts, Nothing to Disclose.

M10. The Risk of Switch to Mania in Patients with Bipolar Disorder during Treatment with Antidepressants Alone and in Combination with a Mood Stabilizer

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Background: Depressive episodes are the most burdensome aspect of bipolar disorderillness and, as such, antidepressants are widely prescribed, even thoughevidence of efficacy is sparse. The use of antidepressant monotherapy is,however, discouraged due to the widely held belief that this confers a risk fortreatment emergent manic episodes. Treatment guidelines submit thatantidepressants should be used in combination with mood stabilizers, althoughevidence that such combinations tangibly diminish risks or improve outcomes islargely lacking.
Methods: Using Swedish national registries, we identified 3,240 people withbipolar disorder who started treatment with antidepressants, without anyantidepressant treatment the prior year. We stratified patients into those thatwere on antidepressant monotherapy, and those on antidepressant plus a moodstabilizer. We used stratified Cox regression analyses to compare the rate ofmania 0–3 and 3–9 months after start of antidepressant medication with apreceding non-treated period. We used a within-individual design to control forconfounding by disorder severity, genetic and early environmental factors.
Results: The increased risk of treatment emergent mania was confined to patientson antidepressant monotherapy [hazard ratio (HR) 2·83, 95% confidence interval(CI) 1·12–7·19]. Patients on a concurrent mood stabilizer displayed asignificantly *decreased* risk of mania 0–3 months after start ofantidepressant treatment (HR 0·64, 95%CI 0·46–0·90) and a suggestive *decreased*risk of mania also after 3–9 months (HR 0·72, 95%CI 0·51-1·03).
Conclusions: The results show that the use of mood stabilizers decreases the risk formania in patients receiving antidepressants for treatment of bipolar depressiveepisodes. The finding that antidepressant monotherapy increases the risk ofmania is in line with previous findings and supportive of current practiceguidelines. Our data do not address whether or not antidepressants effectivelytreat or subsequently prevent bipolar depressive episodes.
Keywords: mood stabilizer, treatment emerging switch, antidepressant, bipolar disorder
Disclosures: M. Landén, Nothing to Disclose; M. Thase, Nothing to Disclose.

M11. Do α2-Containing Nicotinic Acetylcholine Receptors Play a Role in Baseline and Nicotine-modulated Behaviors in Mice?

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Background: The *Chrna2* gene encodes the α2 nicotinic acetylcholine receptor (nAChR) subunit. The α2-containing (α2*) nAChRs are expressed in areas of the brain known to regulate many of the behavioral effects of nicotine, including its effects on learning and memory and also the reinforcing properties of the drug. However, little is known about the contribution of α2* nAChRs to the behavioral effects of nicotine. Here, we provide a comprehensive report on the genetic design and behavioral characterization of the *Chrna*2 null mutant mouse line.
Methods: Targeted deletion of the α2 nAChR subunit was performed by the insertion of a neomycin resistance cassette in exon 5 of the *Chrna*2 gene. Behavioral studies assessed motor, sensory, anxiety, and food reinforcement in the *Chrna*2 null mutant mouse line. Behavioral effects of nicotine were also assessed in the mutant mice, including cued, contextual and trace fear conditioning, intravenous self-administration and somatic and affective measures of nicotine withdrawal.
Results: We found that *Chrna*2 null mutant mice have subtle yet discernible deficits in aspects of motor coordination, nicotine-induced analgesia, nicotine self-administration behavior, and nicotine-induced somatic and affective withdrawal signs. *Chrna*2 null mutant mice also exhibited a sex-dependent enhancement of nicotine-facilitated cued, but not trace or contextual fear conditioning.
Conclusions: These data suggest that the absence of the *Chrna*2 gene in the mouse brain plays a limited role in modifying baseline behaviors but does influence a number of nicotine-facilitated behaviors.
Keywords: nicotinic acetylcholine receptors, memory, withdrawal, self-administration, addiction
Disclosures: S. Lotfipour, Nothing to Disclose; J. Byun, Nothing to Disclose; P. Leach, Nothing to Disclose; C. Fowler, Nothing to Disclose; N. Murphy, Nothing to Disclose; P. Kenny, Nothing to Disclose; T. Gould, Nothing to Disclose; J. Boulter, Nothing to Disclose.

M12. Intraaccumbal Administration of Zeta Inhibitory Peptide (ZIP) Erases Drug Memory and Prevents Cocaine Reinstatement

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Background: During abstinence, memories associated with drug-taking persist and the inability to eliminate these drug memories is thought to underlie addiction. Eliminating these drug-paired memories could provide an opportunity for therapeutic intervention. Converging evidence suggest that zeta inhibitory peptide (ZIP) eliminates memories for experience-dependent behaviors, included conditioned drug associations. However, it is not known whether the elimination of these memories alters drug relapse. ZIP is a synthetic compound designed bind the constitutively active form of atypical PKC, PKMζ, a protein implicated in learning and memory. However, recent evidence from PKMζ knockout mice suggests that ZIP may function through alternative mechanisms.
Methods: The current study examined the effect of ZIP administration in the nucleus accumbens on cocaine-primed reinstatement of cocaine seeking, a rodent model of relapse.
Results: We demonstrate that intraaccumbal ZIP blocks cocaine-primed reinstatement when administered 24-hours or 1 week prior to testing. Interestingly, ZIP infusion has no effect on the reinstatement of food seeking.
Conclusions: Experiments utilizing PKMæ knockout mice are underway to determine whether the effects of ZIP are dependent upon its actions on PKMζ. These results suggest that further examination of ZIP's mechanism of action could provide novel targets for the treatment of cocaine addiction.
Keywords: Cocaine, reinstatement, PKMzeta, addiction, drug memory
Disclosures: L. Briand, Nothing to Disclose; C. Pierce, Nothing to Disclose.

M13. Cocaine Sensitivity is Regulated by Striatal α5-Containing Nicotinic Acetylcholine Receptors

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Background: Allelic variation in the *CHRNA5* gene, which encodes the α5 nicotinic acetylcholine receptor (nAChR) subunit, has been repeatedly associated with tobacco dependence. Paradoxically, the same genetic variation has been correlated with a decreased risk of developing cocaine dependence (*Grucza et al., Biol Psychiatry, 2008*). The role of α5-containing (denoted α5*) nAChRs in regulating the reinforcing properties of cocaine that drive dependence has not been explored. Thus, we sought to investigate whether α5* nAChRs influence cocaine self-administration and/or modulate cocaine's effects on brain reward function. We also investigated whether α5* nAChRs regulate cocaine-mediated neuronal signaling in the striatum, a key brain structure implicated in cocaine reinforcement.
Methods: Mice with null mutation of the α5 nAChR subunit gene (*Chrna5*) and their wildtype littermates were trained to respond for food reward under a fixed ratio 5, time-out 20 s (FR5TO20 sec) schedule of reinforcement during 1-h daily testing sessions. Next, the mice were permitted access to a training dose of cocaine (0.3 mg kg^{-1} per infusion) for intravenous self-administration. After stable responding on the training dose, a full cocaine dose-response function (0.03–3.0 mg kg^{-1}) was characterized according to a Latin square design. A second set of mice were implanted with cranial electrodes and trained in a discrete-trial current-threshold intracranial self-stimulation (ICSS) procedure until stable reward thresholds were obtained. Mice were then injected with varying doses of cocaine (2.5–20 mg kg^{-1}) according to a Latin square design. Finally, striatal sections from a third set of wildtype and α5 knockout mice were examined for baseline and cocaine-evoked alterations in neuronal activity using whole-cell patch clamp electrophysiological recordings.
Results: Wildtype and α5 knockout mice similarly acquired cocaine self-administration at the moderate training dose. However, when a lower dose of cocaine was available, α5

knockout mice increased their cocaine consumption compared to wildtype mice. When brain reward thresholds were assessed, wildtype mice exhibited a 'U' shaped dose response curve, with reward threshold lowering across all of the doses tested. In contrast, the α5 knockout mice displayed a shallower dose response function, suggesting less sensitivity to the rewarding effects of cocaine. Moreover, at the highest dose of cocaine, α5 knockout mice demonstrated an elevated threshold over baseline values, suggesting an aversive/inhibitory effect on brain reward function. The baseline and cocaine-mediated activity of striatal neurons differed dramatically between the wildtype and α5 knockout mice, suggesting that α5* nAChRs modulate cocaine's effects within the striatum.

Conclusions: These data suggest that α5* nAChRs in the striatum regulate the reward-enhancing properties of cocaine and thereby control consumption of the drug. Specifically, deficient expression of α5 nAChR subunits blunted the reward-enhancing effects of cocaine and thus resulted in a compensatory increase in self-administration at a lower dose of the drug, differences which may be attributed to altered cholinergic signaling in the striatum. Together, these findings reveal a fundamental role for α5* nAChR signaling in cocaine reinforcement, may explain the observed protective effects of allelic variation in *CHRNA5* for cocaine dependence, and identify a novel target for the development of therapeutics to treat cocaine addiction.

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Keywords: addiction, nicotinic acetylcholine receptor, α5, cocaine, striatum

Disclosures: C. Fowler, Nothing to Disclose; B. Lee, Nothing to Disclose; P. Kenny, **Part 1:** Scientific consultant for Pfizer, Sharholder in Eolas Therapeutics, Inc.

M14. Exome Sequencing in Rhesus Macaques Exhibiting Individual Differences in Aggression

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Background: Aggression is a behavioral trait that appears to be under selection, as it facilitates access to resources and mating opportunities across mammals, including in primates. However, in humans, exaggerated aggression is known to be a hallmark of a number of psychiatric and personality disorders. The rhesus macaque (*Macaca mulata*) has been used to model some aspects of such disorders and has also been used for identifying functional genetic polymorphisms that predict individual differences in behavior. While the commercially abundant rhesus macaque is one of the most widely used nonhuman primate in biomedical research, few studies have attempted to compare coding-sequence variation between macaque and human, which could further inform its use as a model for human biology, including these behavioral differences. Here, two Indian rhesus macaques, distinguished by marked differences in reactivity and temperament, were characterized for genome-wide protein-coding variation by using commercially available human-exome based pull-down assays and whole exome sequencing.

Methods: Two Indian rhesus macaque subjects that were selected based on being very passive or very aggressive were characterized for genome-wide protein-coding variation. Exploiting the phylogenetically close relationship between human and macaque we leveraged the high degree of sequence similarity between them by using a human-based exon assay (Agilent) on the Illumina Genome Analyzer platform.

Results: Human-on-macaque exon pulldown and sequencing successfully resolved ~80% of the sequences expected from a human-on-human assay. After filtering (depth of coverage > 20; Qscore >100), approximately 274,000 SNPs (Single Nucleotide Polymorphisms) were called, ~94,000 in target regions. 244,670 SNPs were novel as compared to the 2.7×10^6 SNPs reported for macaque in the ensemble variation database (v71). Ts/Tv ratios and distribution percentages were similar to results previously reported in transcriptome sequencing of macaque (Yuan *et al.*, 2012). SNPs, some of which are predicted to be potentially deleterious by *in silico* analysis, were found in the transcribed region of 41 genes and in the coding region of 31 of those, including several behavior-related genes of interest to alcohol-dependence. For verification, six candidate behavior-related genes (*MPDZ, TDRD1, GAL, CRTAC1, GABRA6, CRHR2*) showing non-synonymous SNPs (variants that predicted amino acid changes) in exon capture were verified by Sanger sequencing in 23 additional macaques (in addition to the two exome sequenced individuals).

Conclusions: An advantage of exome sequencing is the immense potential for efficiently identifying functional variants, since only the protein coding sequences are screened for variation. Here we show that cross-species exome capture using off-the-shelf commercially available arrays can be a valuable tool for discovery of functional variation in the rhesus macaque relevant to human disease. This information can help guide animal model development and translational research. In particular, the CRH and the GABA systems are known to relate to stress-induced and escalated aggression in rodents. Our results may support a role for polymorphism at these genes in contributing to individual differences in aggressive behavior in humans and may further support a role for targeting these systems to treat or attenuate aggression and violence in select subjects.

Keywords: whole-exome, rhesus macaque, CRHR2, GABRA6, agression

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M15. Conditional Elimination of the Interleukin-1 Receptor for the Study of the Impact of Inflammatory Cytokines on Brain and Behavior

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Background: Depression is a debilitating disease that accounts for a significant loss in productivity and healthcare costs worldwide. Altered central serotonin (5-HT) signaling have been linked to various psychiatric conditions, including depression, anxiety and obsessive-compulsive disorder and autism spectrum disorder. The presynaptic 5-HT transporter (SERT) limits access of 5-HT receptors to the neurotransmitter in the brain and periphery and is a target for widely prescribed antidepressant medications. The mechanisms by which SERT is regulated under normal and pathophysiological states are poorly understood. We have shown (Zhu *et al*, 2006; Chang *et al*, 2012) SERT to be regulated by a p38 MAPK linked pathway downstream of IL-1 receptor (IL-1R) activation by IL-1β. Application IL-1β to mouse brain synaptosomes *in vitro* results in a rapid stimulation of SERT activity that is lost in IL-1R KO mice. Moreover, peripheral LPS-induced inflammation results in a rapid increase in CNS SERT activity and increased immobility in the tail suspension test, with both effects lost in IL-1R KO mice (Zhu *et al*, 2010). Since IL-1Rs are expressed throughout the body, including the CNS, constitutive IL-1R KO mice are insufficient to determine the site(s) and timing of receptor expression and IL-1β that support 5-HT dependent behavioral changes. To pursue this question, we have generated mice suitable for the conditional elimination of the IL-1R (IL-1R$^{flox/flox}$). These animals will be used in parallel with animals carrying a conditional allele of p38 MAPKα, the key signaling pathway through which the IL-1R regulates SERT activity.
Methods: To generate a *Il1r1*$^{flox/flox}$ allele, we used a conventional homologous recombination approach to insert *loxP* sites flanking the 3rd and 4th exons of the *Il1r1* gene in 129S6 embryonic stem cells. Injection of these cells lead to the generation of chimeric animals that passed the floxed gene through the germline. IL-1R$^{flox/flox}$ animals have been produced that are congenic on a 129S6 background and approaching congenic status on a C57BL/6J background. To determine whether the presence of *loxP* sites is detrimental to IL-1R gene expression, we used quantitative RT-PCR to determine relative IL-1R mRNA expression in both midbrain and spleen of 129S6 IL-1R$^{flox/flox}$ mice and wild type (WT) 129S6 controls. As we wish to pursue the role of the IL-1R in SERT gulation, *ex vivo* 5-HT uptake assays were utilized to measure SERT function in midbrain and frontal cortex synaptosomes from these animals. All animals were housed in AAALAC-approved facilities and experiments were conducted under an approved protocol annually reviewed by the Vanderbilt Institutional Animal Care and Use Committee.
Results: Initial characterization of IL-1R$^{flox/flox}$ mice reveals that these animals are viable, reproduce normally, and display no gross abnormalities. QuantitativeRT-PCR studies reveal no alterations of IL-1R mRNA levels in either midbrain or spleen, consistent with the benign nature of inserted *loxP* sites. Additionally, IL-1R$^{flox/flox}$ animals demonstrate normal paroxetine-sensitive, synaptosomal SERT activity, also seen with p38 MAPK$^{flox/flox}$ mice. Successful, raphe-specific, p38 MAPKα elimination has been achieved using ePET-1 Cre mice (Scott *et al*, 2005) and efforts are now being pursued to use the same approach to eliminate the IL-1R in 5-HT neurons. Intact IL-1R mRNA expression and SERT activity provides an optimum background for evaluation of the actions of the cytokine receptor *in vivo*.
Conclusions: The studies above indicate successful generation of IL-1R$^{flox/flox}$ mice with evidence of normal breeding, growth and morphology. The availability of these mice will allow for the regional and temporal elimination of IL-1Rs, providing a powerful tool to dissect the actions of IL-1β in the brain and periphery. With respect to our goals, these animals will afford a critical opportunity to evaluate IL-1R-mediated p38 MAPK signaling in the activation of SERT at synapses and the role of this activation in 5-HT signaling and behavior. Given the comorbidity of immune system dysfunction with multiple neuropsychiatric disorders, our animal model should have translational relevance, including the examination of immune system-based therapeutics. (NIH R21 MH086033, R01 MH095044)
Keywords: immune system, interleukin-1 receptor, serotonin, serotonin transporter
Disclosures: M. Robson, Nothing to Disclose; C. Zhu, Nothing to Disclose; K. Lindler, Nothing to Disclose; N. Baganz, Nothing to Disclose; J. Wright, Nothing to Disclose; W. Hewlett, Nothing to Disclose; R. Blakely, Nothing to Disclose.

M16. Genes Harboring Addiction-related Variants Alter Dose-response Relationships for Stimulant Reward

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Background: Abused substances typically provide inverted U dose response relationships, thought to represent balances between rewarding and aversive influences of most of these addictive substances. Though classical genetic studies identify substantial heritable influences on addiction-related phenotypes that include quantity/frequency of substance use, there has been little emphasis on the possibility that shifted dose-response relationships for the reward that comes from use of addictive substances might provide substantial impact on the genetic influences on vulnerability to substance use disorders.
Methods: Genes that harbor GWAS associaton signals with groups of nearby SNPs displaying $10–2 > p > 10–8$ association in each of multiple independent human dependent *vs* control samples were identified. Association with level of mRNA expression in postmortem cerebral cortical specimens with SNPs in these genes was assessed using PLINK. Mice with variation in levels of expression of these genes were tested using cocaine conditoned place preference, with control tests of strength, mobility, and memory (Morris water maze and others).
Results: The cell adhesion molecules CDH13 and PTPRD were identified in >12 indepdent samples from GWAS signals that, individually, were below Bonferroni-corrected levels for genome wide significance. Each of these was expressed in postmortem cerebral cortical samples in ways that correlated significantly with genotypes at SNPs located in the 5' ends of the genes. Heterozygous knockout mice for each of these genes displayed remarkably-left-shifted dose response relationships for cocaine conditioned place

preference. Reward from 5 mg/kg doses was greater than that from 10 mg/kg doses (10 mg/kg is optimal in wildtype littermates). Tests of locomotion and memory provided no obvious confounding influences. Literature searches provided remarkably confirmatory support for these shifted dose response relationships from GWAS studies of individual differences in responses to acutely administered amphetamine and description og responses to first alcohol self administrations.
Conclusions: Addiction genetics appears to receive substantial contributions from genetic variants that alter dose response relationships for addictive substances in experimental animals in ways that receive support from human data. Consequences of these shifted dose-response relationships for addiction vulnerability, progression of use of addictive substances, and pharmacotherapeutic approach to addiction have been modestly explored, if at all. Differences in dose response relationships do not play prominent roles in nosology, except for the active interest in alcohol. As more comparable observations are accrued, it will become more difficult not to include explicit assessment of dose-response relationships into thinking about addiction and substance dependence disorders.
Keywords: cocaine, amphetamine, knockout mouse, translational reserach, polygenic disorder
Disclosures: G. Uhl, Nothing to Disclose; F. Hall, Nothing to Disclose; B. Ranscht, Nothing to Disclose; N. Uetani, Nothing to Disclose; J. Drgonova, Nothing to Disclose.

M17. Mother's 5-HTTLPR Genotype X Infant's Genotype Interact to Affect Mother-i Interactions and Developmental Outcomes: Aggression, Anxiety, and Social Behavior

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Background: Thomas and Chess showed that mother-infant interactions can be classified as easy or difficult according to the temperament of both the mother and the infant. It is likely by the genes of the infant and the mother modulate this effect, but studies have to date not assessed how the genotypes of the two interact to affect the infant's developmental outcome. Nonhuman primates are ideally suited to assess such questions both because of their close similarity to humans and because environments can be closely controlled. Using a nonhuman primate model, rhesus macaque (*Macaca mulatta*) mother-infant pairs were longitudinally assessed measuring mother-infant interactions and the infants' behavioral outcomes with other group members.
Methods: Both the mother and the infant were genotyped for the serotonin transporter genotype (5-HTTLPR). In addition, mothers' were classified according to early rearing experiences. In Study 1 ($N = 95$ pairs), naturally occurring mother-infant interactions were assessed weekly for the first six months of life using two 300 s sessions. Study 2—Attachment theorists rate attachment quality according to how an infant responds to reunion after separation. Hence, in Study 2 mother-infant interactions were assessed during mother-infant reunions following four, 4-day social separations ($N = 120$ pairs). Behaviors were reduced to general categories using factor analysis, and factor scores were analyzed using ANOVA. Independent variables included the 5-HTTLPR genotype of both the mother and infant and mothers early rearing.
Results: Study 1 - There were significant infant genotype by mother genotype interactions for distress vocalizations [f(1/98) 3.74, $p < 0.05$]. Mothers' rearing interacted with genotype affecting freezing (a measure of anxiety) [f(2/83) 5.02, $p < 0.01$] and mothers' rearing interacted with mother's genotype to modulate sociality [f(2/83) 4.22, $p < 0.02$]. In addition, only the infants of whose genotype matched their mothers' genotype exhibited aggression. Significant infant genotype main effects were seen for the frequency in which the infants received aggression from other group members [f(2/83) 6.87 $p < 0.01$], with the Ls infants receiving more aggression. Study 2 showed that during mother-infant reunions, infant sociality was affected if both the mother and the infant were heterozygous for the transporter genotype, with both possessing the Ls genotype. Compared to other genotype combinations, infants from MI pairs where both mother and infant had the Ls genotype approached mother more often ($p = 0.03$), and failed to engage in positive social interactions such as grooming with mother or other group members. Furthermore, infants and mothers homozygous for the long genotype (LL) were the only group of infants to display any kind of aggressive defense of status, and these infants were the only ones to engage in social play during reunions.
Conclusions: Our results are the first to our knowledge that have assessed the interaction between parent genotype and offspring genotype as it impacts infant development. Our studies suggest that the mother-infant interaction is more conflict ridden and that infant outcome is less optional when both the mother and the infant possess the short allele. Moreover, infant outcome is modulated by this interaction. We suggest that the underlying mechanism that leads to such negative effects is that the mother's genotype produces a phenotype that leads to a different genotypic-related environment. This in turn affects the infant's genotypic-mediated outcomes. Our findings are consistent with recent studies of aggression showing that the genotype of the perpetrator and victim interact to modulate aggression and suggest a novel way of looking at social interactions.
Keywords: serotonin primate genotype gene X environment early experience
Disclosures: P. O'Connell, Nothing to Disclose; J. Jackson, Nothing to Disclose; S. Lindell, Nothing to Disclose; A. Sorenson, Nothing to Disclose; C. Lindell, Nothing to Disclose; M. Schwandt, Nothing to Disclose; S. Suomi, Nothing to Disclose; C. Barr, Nothing to Disclose; J. Higley, Nothing to Disclose.

M18. Genome-wide Mapping of Complex Psychiatric Traits in Commercially Available Outbred Mice

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Background: Mice offer a powerful tool for elucidating the genetic basis of behavioral and physiological traits with relevance to psychiatric disorders. Identifying specific genes that underlie these traits has proven difficult because their individual contributions are small and because most studies focus on crosses between inbred strains that possess few recombinations. As a result, conventional approaches have only been able to locate large chromosomal regions, but not specific genes. Now, as technologies for genotyping have evolved, it is no longer expensive or difficult to perform GWAS in highly recombinant populations of mice.
Methods: We have taken advantage of an extant outbred population that has been maintained using an outbred breeding scheme for more than 100 generations. We carefully phenotyped 1200 male CFW mice for a battery of behavioral traits including methamphetamine sensitivity, conditioned fear, and prepulse inhibition. Mice were genotyped using a genotyping by sequencing approach (GBS) at ~300k markers across the genome. In addition, we performed RNASeq on three brain regions (prefrontal cortex, hippocampus, and striatum) from a subset of 80 animals.
Results: We conducted a GWAS for the behavioral phenotypes and gene expression traits and identified many significant SNPs that were associated with each trait. For example, we identified 3 SNPs within Frmd4b, Fkbp8, and Nbas that were significantly correlated with startle response on the prepulse inhibition behavioral paradigm. In addition, these genes are all expressed in the adult brain, making them promising candidates for future studies.
Conclusions: By exploiting the increased recombination frequency in outbred mice, we mapped behavioral and gene expression QTLs with greater precision than previous approaches. By identifying single nucleotide polymorphisms (SNPs) that were associated with both behavioral phenotypes and gene-expression traits we can begin to identify plausible biological explanations for how these alleles influence behavior and thereby implicate specific genes. This information can in turn be used to identify alleles that contribute to human psychiatric disease, elucidate causative biological mechanisms, or assist in the development of putative treatment strategies for psychiatric disorders.
Keywords: GWAS, conditioned fear, methamphetamine sensitivity, prepulse inhibition, mice
Disclosures: C. Parker, Nothing to Disclose; N. Gonzales, Nothing to Disclose; A. Palmer, Nothing to Disclose.

M19. A Cross-species Investigation into the Role of Lhx6 in Cortical Inhibitory Circuitry Disturbances in Schizophrenia

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Background: Disturbances in the inhibitory circuitry of the prefrontal cortex (PFC) in schizophrenia are most prominent in the subpopulations of GABA neurons that express the calcium-binding protein parvalbumin (PV) or the neuropeptide somatostatin (SST). Since PFC GABA neurons undergo anatomical, molecular, and synaptic changes across childhood and adolescence, incomplete postnatal development of PFC GABA neurons has been hypothesized as a potential pathogenetic process in schizophrenia. However, reports of incomplete phenotypic specification of PV neurons and arrested migration of SST neurons in the PFC suggest that the disease process may begin earlier, even prenatally, and interfere with the birth, migration, cell-type specification, and/or maturation of these neurons. Consistent with this hypothesis, we recently reported deficits in the cell type-specific transcription factor Lhx6, which selectively regulate the prenatal development of PV and SST neurons, in the PFC in a cohort of 42 schizophrenia subjects. A complete absence of Lhx6 prenatally in mice, albeit more severe than the Lhx6 deficit reported in schizophrenia, leads to reduced tangential migration and impeded differentiation into PFC PV and SST neurons.
However, further investigation into the developmental role of Lhx6 in the pathogenesis of PV and SST neuron dysfunction in schizophrenia requires a translational, cross-species approach. First, we determined whether deficits in PFC Lhx6 mRNA levels are also present in a new cohort of 20 schizophrenia subjects. Second, to determine whether deficits in Lhx6 mRNA in schizophrenia are consistent with a pattern of incomplete postnatal developmental processes, we analyzed the postnatal developmental trajectory of Lhx6 mRNA expression in the PFC of a large cohort of monkeys. Finally, we used mice with an Lhx6 heterozygous null mutation ($Lhx6^{+/-}$) to investigate the extent to which a partial loss of Lhx6 that is more similar in magnitude to that seen in schizophrenia may contribute to other reported disturbances in GABA-related markers in the PFC in schizophrenia.
Methods: Human subjects. Twenty schizophrenia subjects were individually matched to healthy comparison subjects 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 (qPCR) was used to measure Lhx6 mRNA levels in PFC area 9 using the comparative threshold cycle method with four replicate measures per target gene, and target gene expression levels were normalized using three reference genes. Developmental monkeys. Forty-nine rhesus macaque monkeys ranging in age from 1 week to 11.5 years were assigned to four age groups (perinatal, childhood, peripubertal, and adult). RNA was isolated from gray matter of the frontal pole (area 10) due to the availability of existing tissue. Lhx6 mRNA levels were quantified by qPCR as described above. $Lhx6^{+/-}$ mice. Fresh, frozen brains of young adult male $Lhx6^{+/-}$ mice ($n=9$) and wild-type littermate male mice ($n=9$) were obtained from The Jackson Laboratory. RNA was isolated from frontal cortex homogenates, and qPCR for GABA-related markers is being performed as described above. In situ hybridization for PV mRNA with film analysis and cellular grain counting analyses is also being conducted in the medial PFC.
Results: Lhx6 mRNA levels were lower (−13%) in the prefrontal cortex of the new cohort of schizophrenia subjects relative to healthy comparison subjects and were not related to substance abuse, smoking or use of psychotropic medications at time of death. In the cohort of monkeys of different postnatal ages, Lhx6 mRNA levels declined 23% from the perinatal period to childhood then remained stable throughout adolescence and adulthood.

Finally, mean Lhx6 mRNA levels were 45% lower in frontal cortex homogenates of Lhx6$^{+/-}$ mice relative to wild-type littermate mice which is consistent with a loss of gene function in one Lhx6 allele. Studies of additional GABA-related markers by qPCR and in situ hybridization in the Lhx6$^{+/-}$ mice are underway.

Conclusions: In this study, we utilized a cross-species approach to further investigate the role of Lhx6 in the pathogenesis of PFC PV and SST neuron dysfunction in schizophrenia. The replicated finding of deficits in Lhx6 mRNA levels in a new cohort of schizophrenia subjects suggests that low Lhx6 mRNA levels, along with deficits in PV and SST mRNAs, are a common feature and integral part of PFC GABA circuitry dysfunction in schizophrenia. Second, we found that Lhx6 mRNA levels were highest in the PFC postnatally during the perinatal time period and declined until childhood in monkeys, which is consistent with reports of a prominent role of Lhx6 in the early development of PFC PV and SST neurons. In contrast, the stability of Lhx6 mRNA levels across childhood and adolescence suggests that Lhx6 may not be involved in the anatomical and molecular changes in PV and SST neurons that occur during this time period. Finally, employing a mouse model of partial loss of Lhx6 similar in magnitude to that reported in schizophrenia will allow a determination of whether a partial loss of Lhx6 is sufficient to produce the pattern of disturbances in GABA-related markers that has been reported in the illness.

Keywords: GABA, parvalbumin, somatostatin, prefrontal, schizophrenia

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M20. DNA Methylation Network Dysregulation Expressed in Lymphocytes of Schizophrenic Patients

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Background: Epigenetic dysregulation of the brain genome may be associated with the underlying pathophysiology of schizophrenia (SZ) and related psychosis. We and others have previously shown that two enzymes involved in the methylation/demethylation cycle –DNMT and TET are increased in the corticolimbic structures of postmortem brain of schizophrenic patients, and we have previously shown that the brain abnormalities in DNMT1 and 3A are also expressed in peripheral blood lymphocytes (PBL). Other researchers have reported abnormalities in Glucocorticoid receptor (GCORTR) and brain derived neurotropic factor (BDNF) mRNA in the post-mortem brains of SZ. Promoters for these genes are importantly influenced by the extent of DNA methylation. In the current study we examined whether abnormalities in methylation/demethylation mRNA markers and GCORTR and BDNF mRNA are present in PBL of schizophrenic patients and are similar to those which have been found in post-mortem brain samples of SZ. In a related study we also examined the effects of Yoga treatment in schizophrenic patients on these markers.

Methods: PBL were collected from 28 SZ patients and 21 Non psychotic controls (NP) participating in evaluation and treatment studies at NKI, and additional samples were collected at baseline and 3 months of SZ patients participating in a research project with standardized yoga treatment (3 × week) emphahzising Qigong movements and coherent breathing. Lymphocytes were separated by Ficoll-Paque plus centrifugation and RNA isolated by Trizol reagent and Qiagen RNeasy Kit, and converted to CDNA. Real-time polymerase chain reaction (qPCR) was performed using Applied Biosynthesis Real-Time PCR system and Fermentas Maxima SYBR Green/ROX qPCR Master Mix. PCR mixtures were run on a Stratagene (USA) Mx3005P QPCR System. Primers were designed to cross over one intron to amplify cDNA and yield an amplification of between 75–200 base pairs. C_T value was used for relative quantification of target gene expression and normalized to β-actin and the relative expression levels were calculated as C_T. Statistical analysis used t-tests and analysis of variance.

Results: SZ showed a significant 40% decrease in DNMT1 mRNA ($P = 0.01$) and a nearly 50% increase in TET1 ($P = 0.005$) mRNA, and no change in MBD4 mRNA or APOBEC 3A mRNA. The changes in DNMT1, TET1 and MDB4 are similar those we previously reported in post-mortem brain samples of SZ. GCORTR mRNA was decreased by about 50 %($P < 0.001$) and BDNF-IXabcd m RNA was decreased by 32% ($P = 0.055$). Additional analysis suggested that differences in characteristics related to demographic factors, smoking status, and differences in medication treatment were not likely confounds. Three months of Yoga significantly ($P < 0.05$ to $P < 0.01$) decreased DNMT1 and TET1 mRNA IN PBL of SZ. GCORTR mRNA was also significantly decreased in PBL by 3 months of Yoga treatment in SZ.

Conclusions: The finding that the expression of DNA methylating/demethylating enzymes and SZ candidate genes such as BDNF and GCORTR are altered in the same direction in both the brain and PBL support the hypothesis that a common epigenetic dysregulation may be operative in the brain and peripheral tissues of SZ patients. This opens up the possibility that changes in these or other epigenetic related markers may help in investigating the underlying molecular pathology of SZ in living subjects and potential for identifying vulnerability factors in prodromal subjects or those at higher risk. The effects of yoga on decreasing DNMT1 and TET1 in PBLs may point to future research using behavioral techniques to modify abnormalities in the methylation/demethylation pathway.

Keywords: DNAm, schizophrenia, epigenetics, yoga

Disclosures: R. Smith, **Part 4:** Drug supplies for active and placebo varenicline for stanely reserch Foudnation Sup0orted study of vareniclien in schizophrenia; J. Auta, Nothing to Disclose; H. Sershen, , Nothing to Disclose; A.

Lajtha, Nothing to Disclose; S. Boules, Nothing to Disclose; P. Gerbarg, , Nothing to Disclose; R. Brown , Nothing to Disclose; J. Davis, Nothing to Disclose; A. Guidotti, Nothing to Disclose.

M21. Region-specific Alteration of Wnt Signaling in Bipolar Disorders

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Background: Bipolar illness (BP) and schizophrenia (SZ) are devastating mental disorders and although separate entities share many common features and possibly common biological abnormalities. There is some evidence to suggest that abnormalities of Wnt signaling pathway may be associated with the pathophysiology of BP illness and possibly SZ. Glycogen synthase kinase (GSK)-3β and β-catenin are two important components of the Wnt signaling pathway. The activation of Wnt signaling pathway leads to the inactivation of GSK-3β, leading to the accumulation of β-catenin and its subsequent translocation to the nucleus. Treatment with lithium and antipsychotic drugs causes changes in the GSK-3β and β-catenin in the rat brain, suggesting that the alterations of these two components of the Wnt signaling pathway may be involved in the pathophysiology of these illnesses. However, there are few direct studies of GSK-3β and β-catenin in these illnesses. To further examine the role of Wnt signaling pathway in these disorders, we have determined that protein and gene expression of GSK-3β and β-catenin in three brain regions in the postmortem brain obtained from BP, SZ, and normal control (NC) subjects.
Methods: The postmortem brain samples from 16 BP, 16 SZ, and 16 NC (known as the 'McLean 66 cohort') were obtained from the Harvard Brain Tissue Resource Center (HBTRC). The diagnosis of the subjects were made after retrospective review of all available medical records, and extensive questionnaires about social and medical history completed by family members of the donors, and a criteria of Feigner *et al.* (Diagnostic criteria for use in psychiatric research, Arch Gen Psychiatry, 26:57–63, 1972) was used for the diagnosis of SZ, and DSM-III-R10 for the diagnosis of BP disorders. The protein expression of GSK-3β, and pGSK-3β-ser-9 in the cytosol fraction, as well as the protein expression of β-catenin in the cytosol and nuclear fractions of the PFC, cingulate gyrus, and temporal cortex of the BP, SZ, and NC subjects was determined using the Western blot method. The mRNA expression GSK-3β and β-catenin in the PFC, cingulate gyrus and temporal cortex of these subjects was determined using real-time RT-polymerase chain reaction (qPCR).
Results: *Protein and mRNA expression of GSK-3β:* We found that the protein expression of GSK-3β in the cytosol fraction was significantly decreased in the PFC and temporal cortex, but not in the cingulate gyrus of BP subjects compared with NC. GSK-3β protein expression was not significantly different in any of these brain areas of SZ subjects compared with NC subjects. As an index of GSK-3β activity, we determined the pGSK-3β-ser-9 protein expression. When we compared the protein expression of pGSK-3β-ser-9 between these groups, we found that it was significantly decreased in the PFC of BP subjects, but not significantly different in the cingulate gyrus or temporal cortex of BP compared with NC subjects. Protein expression of pGSK-3β-ser-9 was not significantly different in the schizophrenic subjects in any of these areas compared with NC subjects. When we compared the GSK-3β mRNA expression in BP illness and SZ, and found that it was significantly decreased only in the PFC of BP subjects compared with NC subjects. mRNA levels of GSK-3β in the PFC, cingulate gyrus, and temporal cortex in the SZ group were not significantly different from NC subjects. *Protein and mRNA expression of â-catenin:* Since β-catenin levels are regulated by the GSK-3β activity, we determined the protein expression of β-catenin in these three groups of subjects and found that the protein expression was significantly reduced in the cytosol and nuclear fractions of the PFC and temporal cortex, but not in the cingulate gyrus, of BP subjects compared with NC. On the other hand, we observed that the protein expression levels of β-catenin were significantly decreased in the cingulate gyrus, but were not significantly different in the PFC or the temporal cortex of SZ subjects. We also determined the levels of mRNA in BP, SZ, and NC subjects and found that the mRNA expression of β-catenin was significantly decreased in all three brain regions of the BP subjects compared with NC. However, β-catenin mRNA levels were not significantly different in any of the three brain areas of SZ subjects compared with NC.
Conclusions: These results suggest an alteration of Wnt signaling primarily in the postmortem brain of BP subjects. Whereas there appears to be a dysregulation of GSK-3β in BP illness, this dysregulation appears to be region-specific, such that a decrease in GSK-3β was observed only in the PFC and the temporal cortex. On the other hand, it appears that that the Wnt signaling pathway is disrupted in the cingulate gyrus, but not in the PFC or temporal cortex of SZ subjects. Overall these studies suggest region-specific alteration in Wnt signaling in BP illness and SZ.
Keywords: bipolar disorder, schizophrenia, GSK-3β, β-catenin, postmortem brain
Disclosures: G. Pandey, Nothing to Disclose; X. Ren, Nothing to Disclose; H. S. Rizavi, Nothing to Disclose; Y. Dwivedi, Nothing to Disclose.

M22. An Integrated -omics Approach to Understanding Psychoneuroimmunology Crosstalk

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Background: Crosstalk between immune and neural function is an increasingly important area of study for depression. Although the growing number of publications on cytokines and depression during the last ten years indicate the importance of the psychoneuroimmunology crosstalk in mood disorders, the underlying gene regulatory and functional networks are relatively unexplored.

Methods: We performed a systems biology-based integrative computational analysis to study the interactions between molecular components and to develop models for regulation and function of genes involved in mood disorders, and to identify potential candidates for drugs and drug repositioning. Specifically, we performed functional enrichment analyses on manually compiled comprehensive gene lists related to the immune system and major depressive disorder. We also performed network analyses to explore the topological characteristics of these genes in the context of the human protein interactome and gene coexpression and identified novel sub-networks with interconnected immune- and depression-associated genes.
Results: Pathway enrichment analyses revealed that the prostaglandin and leukotriene metabolic pathways and angiotensin signaling pathways are important for genes that are both immune- and depression-associated. Although gene-wise there was not much overlap between the immune- and depression-related gene sets, there were several enriched pathways that were common to the immune-depression and immune gene sets including interleukin and cytokine signaling pathways, TCR signaling, and glypican network.
Conclusions: Our results indicate pathway-sharing and modularity between depression- and immune-associated genes. The shared pathways and interactions among these two categories of genes also suggests that drugs targeting these shared pathways and interaction modules can be potential drug repositioning candidates for relieving depressive symptoms.
Keywords: depression, immunology, prostaglandin, cytokine, bioinformatics
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M23. Key Role of Decreased Vesicular Uptake in the Profound Myocardial Norepinephrine Depletion in Parkinson's Disease

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Background: It is has become increasingly recognized that in Parkinson's disease (PD), in addition to loss nigrostriatal dopamine (DA) neurons, cardiac sympathetic neurons are also a target of the degenerative process. In the brain there is a discrepancy between the extent of loss of substantia nigra dopaminergic neurons (only about 60%) and the extent of decrease in putamen dopamine content (well over 90%), suggesting functional abnormality in the residual terminals. The same might apply in the heart. The present study was to determine whether neurochemical analysis of post-mortem myocardial tissue samples, along with previously published data about spillover of norepinephrine (NE) and its metabolites into cardiac venous plasma and about the disposition and metabolism of ^{3}H-NE in healthy subjects, could be used to quantify differences between PD and controls in vesicular uptake and oxidative deamination of intra-neuronal catecholamines in myocardial sympathetic nerves.
Methods: Most of the post-mortem left ventricular myocardial tissue samples from PD patients and controls were obtained from the Banner Sun Health Research Institute or autopsies at the NIH. We measured myocardial tissue contents of DA, NE, and their deaminated metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and 3,4-dihydroxyphenylglycol (DHPG). Frozen samples were homogenized in a mixture of 20:80 of 0.2 M phosphoric:0.2 M acetic acid and the supernate transferred to plastic cryotubes and stored at $-80\ ^{\circ}$C until assayed by batch alumina extraction followed by liquid chromatography with series electrochemical detection. Based on a previous study from our laboratory (Eisenhofer *et al*, Circulation 1996; 93:1667–1676) that included estimates of the rates of transfer and metabolism of DA and NE in cardiac sympathetic nerves, we derived fractional rate constants and applied them to calculate rates for the processes involved in the synthesis and disposition of catecholamines in cardiac sympathetic nerves and evaluate determinants of myocardial NE depletion in PD.
Results: We found a striking decrease in NE content of the heart tissue obtained from PD patients. The concentration of NE in myocardial tissue from 15 PD patients was only 2.5% that in tissue from 17 controls (0.0417 ± 0.013 *vs* 1.664 ± 0.289 pmol/mg wet weight). Interfering chromatographic peaks in 5 PD myocardial tissues limited to 9 the number of samples in which both NE and DHPG were measured. In those, the NE concentrations were even lower than in the whole group of PD samples (0.0270 ± 0.0132 pmol/mg). The DHPG levels averaged 0.0095 ± 0.0025 pmol/mg compared to 0.0960 ± 0.0249 pmol/mg in controls. Thus, DHPG:NE ratios in PD were 6.1-fold greater in the PD than in control myocardial tissue. Ratios of DOPAC:NE in PD were 17 times and DOPAC:DHPG 3.7 times those in controls.
Conclusions: We used the equations that define the kinetics of vesicular uptake of DA and NE, NE leakage into the cytoplasm or reuptake after exocytotic release, metabolism of the cytoplasmic amines and the rate constants for the various processes to measure differences between PD and controls in these processes. The greater ratio of DHPG:NE in PD reflected a shift in the fate of cytoplasmic NE from vesicular uptake to deamination as well as the increase in NE turnover rate. Since almost all NE ffopmed in the sympathetic neurons is metabolized to DHPG, the rate of formation of DHPG, and its levels, should not be affected greatly by diminished VMAT. DHPG levels are a better index of NE formation than NE levels. The increase in the DHPG:NE ratio (474%) in PD is primarily due to a fall [n NE because of failure to recapture leaked NE, which is

converted to DHPG. The much lower levels of DHPG in PD (13% of control) probably reflect decreased NE formation from DA and loss of sympathetic neurons. The 3.7-fold greater DOPAC:DHPG ratios in PD reflect decreased NE formation from DA and a shift in DA disposition from vesicular uptake to oxidative deamination. The DOPAC levels in PD averaged 43% those of controls, indicating a much higher level of DOPAC in residual sympathetic neurons in PD than in controls. The combined increase in NE turnover and decrease in NE formation ($1/4.47 \times 1/3.7 = 5.7\%$) accounts for the observed 94.3% fall in myocardial NE content. An estimated a 58% loss of neurons, close to that observed using neuronal markers, is necessary to account for the additional fall in NE levels to only 2.5% of control. In conclusion, the discrepancy between the loss neuronal markers of catecholaminergic neurons in the heart, and probably in the brain, is the result of a deficiency in vesicular uptake. There is a shift from vesicular storage to oxidative deamination. Because of the normal high efficiency of vesicular uptake, even a relatively small decrease in efficiency can produce large changes in formation of aldehydes. For example, a decrease from 92% to 84% efficiency will double the rate of oxidative deamination of catecholamines. Furthermore, since only the dihyroxyphenyacetaldehyde (DOPAL) from DA would be formed in excess, it is likely that this aldehyde would be the responsible agent for toxicity in both dopaminergic and noradrenergic neurons. Thus, vesicular uptake plays a key role in maintaining adequate reserves of myocardial sympathetic neuronal NE and perhaps in limiting formation of toxic aldehydes.

Keywords: Norepinephrine, Dopamine, VMAT, myocardium, MAO

Disclosures: I. Kopin, Nothing to Disclose; P. Sullivan, Nothing to Disclose; D. Goldstein, Nothing to Disclose.

M24. Chondroitin Sulfate Proteoglycan Abnormalities in Schizophrenic and Bipolar Disorder Subjects

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Background: Increasing evidence points to the involvement of chondroitin sulfate proteoglycans (CSPGs) in schizophrenia (SZ). CSPGs are one of the main components of the extracellular matrix (ECM) and are critically involved in processes that shape neural circuits, including migration of neurons and guidance of axons, trafficking of NMDA receptors, glial cell differentiation, and regulation of plasticity and neuronal firing properties, all relevant to the pathophysiology of SZ. Glial cells are main sources of ECM CSPGs. Notably, during late postnatal development, coinciding with the age of onset of SZ, they contribute to the assemblage of perineuronal nets (PNNs), specialized ECM aggregates enriched in CSPGs. Once formed, PNNs stabilize successful neural connections and modulate neuronal functions. In the medial temporal lobe of SZ subjects, we previously reported large increases of CSPG expressing glial cells accompanied by reductions of PNNs. Similar findings in the prefrontal cortex and olfactory epithelium suggest that CSPG abnormalities are widespread. Reported associations of genetic polymorphisms of CSPG genes including PTPRZ1, neurocan, and neuroglycan-C, along with animal studies showing the involvement of CSPGs and their sulfation patterns on brain development and adult functions, lend further support for their involvement in SZ. CSPGs are composed of core proteins with varying numbers of chondroitin sulfate (CS) chains. These chains vary in their patterns of sulfation, which modify their ability to interact with other molecules including growth factors and cytokines, and have significant effects on brain development and adult functions. The two most common sulfation patterns in the brain are 4-sulfation and 6-sulfation. The 4/6 ratio of sulfation is developmentally regulated and increases with the closure of critical periods and the formation of PNNs. The CSPG aggrecan is highly enriched in PNNs, and contains a high amount of CS chains with a predominant 6-sulfation pattern, suggesting that it may play an important role in PNN functions. Aggrecan expression and 6-sulfation in glial cells have been reported to regulate cell differentiation. With the present postmortem study, we tested the hypothesis that CS-6 sulfation patterns on various core proteins, as well as the core protein aggrecan, contribute to CSPG abnormalities in SZ.

Methods: Antibodies raised against aggrecan (cat-301) and CSPGs containing CS-6 sulfation patterns (3B3 and CS56) were used to label immunohistochemically glial cells and PNNs in the amygdala of control ($n = 12$), SZ ($n = 12$), and BD ($n = 13$) subjects. Numerical densities (Dn) and total numbers (N) of immunoreactive (IR) PNNs and glial cells were counted, blind to diagnosis, using computer-assisted light microscopy; group differences were tested using stepwise linear regression models.

Results: In subjects with SZ, aggrecan-positive PNNs were decreased selectively in the lateral nucleus (LN) (N, $p = 0.03$; Dn, $p = 0.03$), where they were primarily located. PNNs labeled with 3B3 were distributed across all amygdala nuclei, and were significantly decreased in the amygdala (N, $p = 0.002$; Dn, $p = 0.002$). Decreases were significant for individual amygdala nuclei as well. Aggrecan-IR glial cells were decreased in the amygdala of SZs (N, $p = 0.02$; Dn, $p = 0.07$), along with 3B3-IR glia (N, $p = 0.005$; Dn, $p = 0.007$), and CS56-IR glia (N, $p = 0.02$; Dn, $p = 0.03$; corrected for effect of selective serotonin reuptake inhibitors (SSRIs)). In BD subjects, N but not Dn of aggrecan-IR PNNs were decreased in the LN ($p = 0.04$); reductions of aggrecan-IR PNN N ($p = 0.04$) and Dn ($p = 0.03$) were also detected in the accessory basal nucleus. Decreases of 3B3-IR PNNs were also observed in the amygdala of BD subjects (N, $p = 0.01$; Dn, $p = 0.02$). In contrast to SZ subjects, no changes were observed in aggrecan-IR glial cells in BD. Decreases in 3B3-IR glia (N, $p = 0.04$; Dn, $p = 0.04$; corrected for effect of lithium), and CS56-IR glial (N, $p = 0.007$, Dn, $p = 0.02$; corrected for effect of lithium), where observed in BD.

Conclusions: Our results show aggrecan and CS-6 sulfation PNN and glial abnormalities in the amygdala of SZ and BD subjects. Decreases of glial cells expressing CS-6 sulfation patterns are in sharp contrast to large increases of glial cells labeled with a broad spectrum CSPG histochemical marker previously observed in SZs. These findings indicate that CSPG abnormalities are more widespread than initially

thought and may affect distinct glial cell populations. Notably, differences between the two disorders were observed. In SZ, reductions of aggrecan and 3B3-IR PNNs in LN, together with previously reported decreases of WFA-positive PNNs in the same nucleus, suggest PNN loss. In BD, decreased aggrecan and 3B3-IR PNNs in absence of similar changes detected by WFA labeling suggests PNN composition anomalies. Decreases of glial cells expressing CS-6 in both SZ and BD indicate that 6-sulfation on these cells may differentially contribute to the changes in PNNs observed in these disorders. Significant statistical effects of SSRIs and lithium on CS56 measures indicates that CS56 changes may occur more prominently in subjects with affective symptoms, and may represent a potential therapeutic target. In SZ and BD, CSPG abnormalities may critically contribute to a disruption of developmental and adult neuronal functions such plasticity and oscillatory rhythms.

Keywords: schizophrenia, bipolar disorder, perineuronal nets, amygdala, glial cells

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M25. CSF and Plasma Interleukin-6 and Personality Traits in Suicide Attempters

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Background: Dysregulation of inflammation has been reported in depression and recently in suicidal behavior. Impulsivity and aggression are part of the suicide phenotype. High levels of neuroticism, and low levels of conscientiousness assessed with structured personality inventories have previously been associated to increased levels of plasma IL-6, in population based samples.The aim of this study was to assess if plasma and cerebrospinal fluid (CSF) levels of IL-6 were associated to personality traits in suicide attempters.

Methods: Plasma and CSF levels of IL-6 were measured in suicide attempters (plasma = 58, CSF = 43) using antibody-based immunoassay systems. Personality domains were assessed using the Karolinska Scale of Personality (KSP). Regression models for the domains of personality were assessed in relation to cytokine levels in plasma and in CSF.

Results: Plasma IL-6 was significantly positively correlated to the personality factor extraversion ($r = 0.48$, $p < 0.0001$) and the subscales impulsivity and monotony avoidance. The regression model remained significant after adjusting for age. CSF IL-6 was associated with monotony avoidance ($r = 0.35$, $p < 0.05$). Plasma and CSF levels of IL-6 were not significantly correlated.

Conclusions: The role of impulsive-aggressive behaviour in suicidality is recognized in several studies, and seems to play a role mostly among younger subjects with suicidal behaviour.The neuroinflammation hypothesis of suicidal behaviour may in part be explained by the positive association between IL-6 and impulsivity, a key part of the suicide phenotype.

Keywords: IL-6, neuroinflammation, suicide attempt, impulsivity, monotony avoidance

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M26. Body Mass Index Affects Brain Dopaminergic Signaling after Glucose Ingestion

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Background: Excessive consumption of of palatable food can lead to obesity, which, in turn, can result in metabolic adaptations perpetuating excessive food consumption. The rewarding effects of food are mediated by its palatability and its energy content. Indeed, gastric administration of sugar or fat increases dopamine (DA) in the striatum (including the nucleus accumbens) can result in overeating because of adaptation to the exposure to high caloric intake. Here we tested the hypothesis that in obese individuals the DA response to calorie intake (independent of its palatability) might be attenuated. We used PET to assess the effects of body mass index (BMI) on brain DA function, contrasting the effects of sucralose (artificial sweetener devoid of calories) to that of glucose to control for the somatosensory stimulation of sweet receptors.

Methods: Nineteen healthy subjects with BMI from 21 to 35 were scanned with [C-11]raclopride after oral ingestion of glucose- and sucralose drinks. Striatal DA D2 receptor availability (DRD2) was analyzed with SPM8 after transforming the voxels in PET images into non-displaceable binding potential (BP_{ND}). The differences between DRD2 availability after the glucose and the sucralose intake (delta BP_{ND}) were used to estimate DA changes secondary to calorie content of glucose. Statistical significance of the voxelwise correlation analyses between BMI and delta BP_{ND} (glucose minus sucralose) was set as PFWE < 0.05, accounting for multiple comparisons with familywise error and small volume (10-mm radius spherical volume) corrections. Pearson correlations were used to evaluate potential linear associations between differences in DRD2 availability (delta BP_{ND}) measured after glucose- and sucralose challenges and the behavioral measures (comprising Three Factors Eating Questionnaire-TFEQ and Gormally Binge Eating Scales-GBES).

Results: The blood glucose levels did not vary as a function of BMI either after the glucose or the sucralose challenge. The correlation between BMI and delta BP_{ND} (glucose—sucralose) was significant in the ventral striatum ($p < 0.001$, PFWE < 0.004), such that the lower the BMI the greater the DA increases, whereas the higher the BMI the greater the DA decreases. In turn, delta BP_{ND} in ventral striatum significantly correlated with the measures of eating behavior; specifically, TEFQ-disinhibition ($r = 0.52$, $p < 0.02$), TEFQ-hunger ($r = 0.6$, $p < 0.006$), GBES ($r = 0.61$, $p < 0.006$), such that subjects with greater disinhibition

(prone to respond rapidly to eating and food opportunities) and greater binge eating scores have lower DA release.
Conclusions: We showed that in individuals with normal BMI caloric value of the food increase DA in the ventral striatum independently of palatability, and that with increase in BMI, these responses get disrupted, resulting in the opposite pattern (DA decreases with the highest BMI). An association of the magnitude of the increase of DA in ventral striatum with the behavioral measures suggests that abnormal striatal DA responsivity to caloric challenge might contribute to excessive food intake.
Keywords: PET, Dopamine, BMI, glucose, caloric
Disclosures: G. Wang, Nothing to Disclose; N. Volkow, Nothing to Disclose; D. Tomasi, Nothing to Disclose; A. Convit, Nothing to Disclose; C. Wong, Nothing to Disclose; E. Shumay, Nothing to Disclose; J. Fowler, Nothing to Disclose.

M27. Abnormal Bioenergetics in Schizophrenia and Bipolar Disorders Studied by Dynamic 31P-MRS

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Background: Schizophrenia (SZ) and Bipolar disorders (BP) are common and severe brain disorders often associated with poor functional outcome. Numerous evidences suggest that patients with SZ and BP exhibit mitochondrial and bioenergetic abnormalities (1), for instance, dysfunctional oxidative phosphorylation (2), aberrant mitochondrial morphology and location (3), and altered mitochondria related gene expression (4), which were observed in *postmortem* studies. Abnormal bioenergetics were also observed using conventional ^{1}H- and ^{31}P- magnetic resonance spectroscopy (MRS) (5,6) via measuring steady-state concentrations of metabolites involved in energy metabolism. Because energy metabolism is essential for metabolic pathways and for neurotransmitter cycling in the brain, abnormalities in these processes would impact all aspects of brain function. *In vivo* probes of mitochondrial function and cerebral bioenergetics could provide crucial information to characterize the exact bioenergetic abnormalities and delineate their relationship to pathophysiology and symptom presentation. In this study, dynamic ^{31}P-MRS novel approaches such as ^{31}P-magnetization transfer (^{31}P-MT) and functional stimulation (^{31}P-fMRS) were applied to accomplish these goals.
Methods: Four groups of participants consisting of patients with SZ and BP, and corresponding age- and sex-matched healthy controls (HC) without any psychiatric disorder including substance abuse/dependence were recruited for these studies (^{31}P-MT and ^{31}P-fMRS for SZ and BP, respectively). SZ and BP patients were screened with a series of standard psychiatric diagnostic and research scales. ^{31}P-MT and ^{31}P-fMRS related acquisitions were conducted using a 4 T whole-body scanner interfaced with a Varian INOVA console. Brain anatomic imaging and ^{31}P-MRS were acquired using two separate, custom-designed dual-tuned surface coils for the frontal lobe and occipital lobe, respectively (see Figs 1 and 2). In the ^{31}P-MT experiment, which has been described in a previous publication (7), the forward chemical exchange constant (k_f) of the creatine kinase reaction (CK) was measured from the frontal lobe ($6'6'4\ cm^3$). ^{31}P-fMRS from the visual cortex was performed on BP patients and healthy controls with a visual stimulation (checkerboard image flashing at 8-Hz) over 30 min with 6 min rest-baseline, 12 min stimulation and 12 min recovery.
Results: There were substantial and statistically significant reductions in both CK k_f and intracellular pH in patients with SZ. The concentrations of most phosphate-containing compounds were not substantially altered in these patients, with the exception of a reduction in the PDE indicated by the PDE/β-ATP ratio. The relative changes of energy substance levels of PCr and ATP have distinctly different patterns during visual stimulation and post-recovery. The ATP signal was relatively stable at short period stimulation then decreased with long in the HC during visual stimulation, but less so in the BP patients. The PCr signal decreased with visual stimulation for HC but not for BP.
Conclusions: Using novel ^{31}P dynamic MRS approaches, we provide the first direct and compelling *in vivo* evidence for specific bioenergetic abnormalities in SZ and BP patients. Reduced k_f of the CK reaction in patients with SZ is consistent with *postmortem* studies that have identified abnormalities in CK enzyme activity (8) and oxidative phosphorylation (4) as well as mitochondria-related genes and gene expression (5). The intracellular pH reduction suggests a shift from oxidative phosphorylation towards glycolysis, providing convergent evidence for bioenergetic abnormalities in these patients. Additionally, reduced CK k_f while the concentrations of ATP and PCr at baseline remained relatively stable suggests that the machinery of energy metabolism is dysfunctional in SZ, but that compensatory measures of energy production at baseline is sufficient to approximate those seen in the HC. However, at times of high demand, ATP availability might be compromised because CK transfers high energy phosphates from storage in PCr to ATP to preserve relatively stable ATP levels needed for maintaining constant neural activity. The hypothesis of a breakdown in energy production in disease during times of high demand is testable because the ^{31}P-MRS approach can be coupled with sensory or cognitive stimulation paradigms. We conducted ^{31}P-fMRS with visual stimulation in patients with BP disorders and found that the energy substance levels exhibited a significantly altered pattern during visual stimulation and recovery. In contrast to the HC, BP patients experienced a reduction in visual evoked reduction in PCr suggesting compromised neuronal response and mitochondrial function. This finding provides greater insight into cerebral activity and bioenergetic metabolism and may provide a new biomarker of brain energy deficits in BP patients.Mitochondrial and other bioenergetic abnormalities have been widely studied using a conventional MRS approach via measuring the steady-state energy substance levels, which depend on the balance between energy generation and utilization and are modulated by multiple metabolic pathways. However, the exact molecular abnormalities are difficult to pinpoint by this approach and as such, there are many discrepancies in the literature. It is clear that conventional MRS approaches are not sensitive enough to measure the subtle but important

changes in brain energy utilization in patients with psychotic disorders and so the present study using a dynamic ^{31}P-MRS strategy possesses several advantages, the most important of which is that the absolute enzyme activity/chemical reaction rate from specific pathways is accessible and/or the relative substance level can be measured after a rather simple stimulus paradigm.
Keywords: Bioenergetics, schizophrenia, bipolar disorder, 31P MRS
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M28. Expression of CHRNA7 and the Chimeric Gene CHRFAM7A are Altered in the Postmortem Dorsolateral Prefrontal Cortex in Major Psychiatric Disorders

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Background: *CHRNA7* (chr 15q13.3) codes for the α-7 nicotinic acetylcholine receptor (α7 nAChR) thought to have a functional role in cognition via interneuron modulation of dopamine and glutamate signaling. α7 nAChRs mainly act presynaptically in the brain, although they exist at both pre- and postsynaptic sites. *CHRNA7* and its partially duplicated chimeric gene *CHRFAM7A* have been implicated in schizophrenia through linkage and association studies, as well as in smoking. *CHRFAM7A* is unique to humans, and expressed in human brains at approximately 10-fold lower levels than *CHRNA7*. Data on the expression of these genes in mental disorders are inconsistent.
Methods: We investigated the expression of *CHRNA7* and *CHRFAM7A* mRNA in the dorsolateral prefrontal cortex in a large cohort of patients with schizophrenia ($n=176$), bipolar disorder (n-61) and major depression ($n=138$) as well as controls across the lifespan ($n=220$) using quantitative real-time PCR with Taqman assays (ABI), and examined the effects of smoking history and/or the presence of nicotine at death as well as medication on gene expression. Finally, we explored the associations between eighty one *CHRNA7* SNPs obtained from Illumnia BeadArrays (1MDuo) and expression levels of *CHRNA7* and *CHRFAM7A*.
Results: Developmental expression patterns of *CHRNA7* and *CHRFAM7A* differed markedly. Expression levels of *CHRFAM7A* were significantly higher in the fetal *vs* postnatal samples ($p<0.05$), whereas *CHRNA7* was more stable throughout life. Expression levels of *CHRFAM7A* were significantly elevated in all three diagnostic groups as compared with controls ($p<0.05$). Expression of *CHRNA7* was reduced in schizophrenia as compared to controls ($p<0.0001$), and increased in patients with major depression ($p<0.0001$). Overall, there was no effect of nicotine or medication on gene expression. Moreover, we did not detect significant effects of SNPs in CHRNA7/CHRFAM7A on expression of *CHRNA7* and *CHRFAM7A*.
Conclusions: Human specific CHRFAM7A is preferentially expressed in fetal samples, suggesting it may play a role in development of the prefrontal cortex. Our data indicate abnormalities in CHRNA7/CHRFAM7A in mental illnessbut the mechanisms of these changes remain elusive.
Keywords: prefrontal cortex, human, nicotinic receptor, postmortem, SNP, genetic
Disclosures: Y. Kunii, Nothing to Disclose; T. Hyde, Nothing to Disclose; A. Deep-Soboslay, Nothing to Disclose; D. Weinberger, Nothing to Disclose; J. Kleinman, Nothing to Disclose; B. Lipska, Nothing to Disclose.

M29. Neural Correlates of Response Inhibition and Concentration of Glutamate/GABA in the Anterior Cingulate Cortex in Borderline Personality Disorder

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Background: High impulsivity and hypo-activation in frontal brain areas including the anterior cingulate cortex (ACC) have been consistently reported in Borderline Personality Disorder (BPD). Recent research further suggests that a high glutamate to GABA ratio in the ACC is an important neurobiological marker of impulsivity. However, to our knowledge, studies investigating glutamate/GABA ratio in the ACC in patients with BPD are lacking. Moreover, studies linking neurobiological markers of impulsivity to subjective and behavioral measures of impulsivity in patients with BPD are needed to further clarify the nature of impulsivity in this disorder.
Methods: Our sample comprised 20 female patients with BPD and 20 female age-matched healthy controls (HC). In-vivo single voxel 1 H MR-spectroscopy (MRS) was conducted at a 3.0 T MR-scanner. The ACC voxel (40x30x20 mmł) was placed based on an isotropic 1 mmł mprage data set with reconstructed coronal and transverse planes aligned with the shape of the corpus callosum. After MRS, participants performed an impulse control task during functional magnetic resonance imaging (fMRI). In addition, a broad battery of self-reports on impulsivity was applied. Statistical correlations between self-reports and neurobiological measures (brain activation, glutamate/GABA ratio in the ACC) were conducted.
Results: Patients with BPD reported significantly higher impulsivity, including impulse control deficits, than HC. No significant differences in behavioral performance on the impulse control task were observed between groups. However, significantly less activation in brain areas such as the inferior frontal gyrus and significantly increased activation in basal ganglia and in the orbitofrontal insula (among others) were found in BPD patients compared to HC. Self-reported impulsivity (BIS scores) was positively correlated with the ratio of glutamate/GABA. Mean GABA value in the ACC was significantly reduced in BPD patients compared to HC.
Conclusions: In line with other studies, we observed higher self-reported impulsivity and frontal hypo-activation but no behavioral deficits during an impulse control task in patients with BPD compared to HC. Increased activation

in a subcortical loop (including the basal ganglia) might be a compensatory mechanism to prevent the occurrence of self-perceived impulse control deficits on a behavioral level in individuals with BPD. As a significant novel finding, we revealed decreased GABA in the ACC in patients with BPD compared to healthy controls. As the ACC is a key region to emotional control, stronglyconnected to the limbic system, decreased GABA concentration may be related to self-perceived difficulties in control mechanisms in BPD.

Keywords: impulsivity, glutamate, GABA, borderline personality disorder

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M30. Measuring the Effects of Acute Alcohol Infusion on Human Brain Metabolites: An MR Spectroscopy Study

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Background: Brain microdialysis studies have in general shown that acute alcohol suppresses glutamate release, while alcohol withdrawal leads to progressively increased extracellular levels. Acute administration of alcohol can lead to both positive (rewarding/stimulating), and negative effects in an individual. The positive effects, such as euphoria and increased verbal activity, occur when blood alcohol concentration (BACs) are rising or at their peak. In contrast, negative effects like sedation and depression generally occur during the period of falling BACs (Lewis 1996; Risinger and Cunningham 1992). The modulation of glutamatergic transmission may contribute to alcohol intoxication, reinforcement, tolerance, and dependence, while drug effects that influence glutamatergic transmission may mediate therapeutic efforts to treat alcoholism (Spanagel and Keifer, 2008). Acute alcohol intoxication in non-dependent animals has generally been reported to suppress glutamate release, while alcohol withdrawal and a history of alcohol dependence have been shown to lead to increased central glutamate levels. Alcohol dependence appears to induce progressive neuroadaptations within the glutamatergic system, and these have been proposed to contribute to the pathophysiology of alcoholism (Spanagel and Kiefer, 2008; Heilig *et al*, 2010). Repeated cycles of alcohol intoxication were reported to result in progressively increasing elevations in extracellular hippocampal glutamate; this consequence of withdrawal was prevented by acamprosate treatment (Dahchour *et al*, 2003). It is presently unknown how local tissue alcohol and glutamate levels are related to each other in humans, whether this relationship is associated with the subjective alcohol effects, and whether level of prior alcohol consumption influences these relationships. There are to our knowledge no human studies that have related brain alcohol exposure to changes in measures of central glutamate. Studies that are available regarding central alcohol effects (Biller *et al*, 2009; Melendez *et al*, 2005) are limited by the fact that none of these studies attempted to measure metabolite concentration under pharmacokinetically controlled conditions, such as those achieved using an intravenous (IV) alcohol administration to a pre-determined, steady state BAC (Gilman *et al*, 2008). An MRS study using oral alcohol administration found only a moderate correlation between blood alcohol concentration (BAC) and brain alcohol concentrations (Fein and Meyerhoff, 2000). The present study is designed to address several of these questions, by bringing human subjects to a steady state BAC of 0.08 g/dl while using MRS scans to measure the concentrations of alcohol, glutamate and other brain metabolites in the subject's brain.

Methods: Here, we have used an acute, pharmacokinetically controlled alcohol challenge and magnetic resonance spectroscopy (MRS) to study the relationship between brain alcohol and glutamate concentrations. We collected spectra from the ACC voxel, a homogenous grey matter region which is implicated in alcohol abuse and alcohol dependence. Healthy participants aged 21–45, without gross impairment of judgment or complicated psychiatric or other morbidity, received a preliminary infusion to ensure no adverse effects from intravenous (IV) alcohol administration to a target BAC of 0.08g/dl. In a subsequent session, participants were infused with alcohol to the same target level while being scanned in the MR scanner. Two groups of subjects were recruited: heavy drinkers, classified as females who consumed 15+ drinks per week and males who consumed 20+ drinks per week, and light drinkers, classified as females who consumed between 1 and 10 drinks per week and males who consumed between 1 and 14 drinks per week.

The current results include data from 16 subjects (4 male Light Drinkers and 2 male heavy Drinkers). MRS was performed on a Siemens Skyra 3 T scanner using the acquisition parameters TR 2000 ms, TE 30 ms, 128 averages, and Flip angle 90 deg. Measurement was made from a $2.5 \times 2.5 \times 2.5$ cm3 voxel in the area of anterior cingulate. MRS data was analyzed using LCModel software (Provencher 1993), which estimates the concentration of metabolites relative to unsuppressed water reference signal.

Results: Our preliminary results not surprisingly indicate significant differences ($p < 0.03$) between brain Ethanol/NAA concentration ratio before and after infusion (mean 0.21 *vs* 1.61). However, there was no difference in pre- and post-infusion Glutamate/NAA ratio (1.01 *vs* 1.05). When separating the only two Heavy Drinkers in current data set, the Light Drinkers had higher Glutamate/NAA ratio than Heavy Drinkers both before and after the infusion. Interestingly, the Light Drinkers had higher Glutamate/NAA ratio after the infusion. But, the Heavy Drinker subjects had decreased Glutamate/NAA ratio after the infusion.

Conclusions: Consistent with the pre-clinical data and clinical studies, ours results for heavy drinkers showed decreased Glutamate/NAA ratio after the acute alcohol infusion. This finding is also consistent with the effects chronic use of alcohol in alcohol dependent patients. The results need to be further verified once more Heavy Drinkers are recruited.

Keywords: MRS, ethanol, glutamate, alcoholism

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V. Ramchandani, Nothing to Disclose; R. Momenan, Nothing to Disclose.

M31. Morphological Alterations in Layer 3 Pyramidal Cells of the Dorsolateral Prefrontal Cortex in Schizophrenia: Role of Actin Cytoskeleton

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Background: Disturbances in the circuitry of the dorsolateral prefrontal cortex (DLPFC) appear to contribute to the pathophysiology of the cognitive deficits in schizophrenia. In particular, pyramidal cells, the principal source of cortical glutamate neurotransmission, exhibit morphological alterations in schizophrenia. These alterations include a smaller somal size, a less complex dendritic arbor and a lower density of dendritic spines. This pattern of pathology is particularly marked in pyramidal neurons located in layer 3, and may reflect an intrinsic deficit in the expression of genes that regulate the actin cytoskeleton in these neurons. This notion is supported by limited data demonstrating that subjects with schizophrenia exhibited altered DLPFC gray matter levels of transcripts in the Rho family of GTPases (e.g., CDC42) which regulate the organization of the actin cytoskeleton. The goal of the present study was to examine in more detail the molecular mechanisms that may contribute to the morphological alterations, especially the lower density of dendritic spines, present in layer 3 pyramidal neurons in the DLPFC of subjects with schizophrenia. Focusing on gene expression in a particular population of neurons may be particularly informative since measures of transcript levels in total gray matter or even individual cortical layers may be diluted by unaffected cell types.
Methods: Individual pyramidal cells (approximately 400 cells per subject) in layer 3 of DLPFC area 9 were captured using laser microdissection from postmortem brain specimens from 19 subjects with schizophrenia and 19 matched healthy comparison subjects. Pyramidal cells were identified based on their characteristic morphology (ie, well defined triangular shape and prominent apical dendrite) in Nissl-stained sections. Total RNA was isolated and converted to cDNA using the QScript^{TM} cDNA SuperMix. Levels of transcripts for the intracellular interacting partners of the CDC42 pathway (*CDC42*, *CDC42EP4*, *PAK1*, *PAK2*, *LIMK1*, *LIMK2*, *ACTR2*, *WASL* and *ARHGDIA*) were quantified using RT-PCR using Power SYBR green dye and ABI StepOnePlus Real-Time PCR system. The transcripts were selected using the GeneMANIA prediction algorithm which allowed us to construct a pathway for CDC42 based on known genetic and physical interactions, co-expression patterns, co-localization patterns and protein domain similarity data. For data analysis, the comparative threshold cycle method was used in which transcript levels were normalized values to the geometric mean of 3 reference genes (*ACTB*, *GAPDH* and *GNAS*) which were included based on their stable expression across schizophrenia and comparison subjects in previous microarray studies.
Results: Our findings revealed several alterations in the intracellular mediators of dendritic spine dynamics. We found a lower expression of upstream regulatory molecules such as *CDC42*, *PAK1* and *WASL* which are the primary mediators of actin remodeling following influx of calcium through NMDA receptors. For example, the mRNA expression levels of *CDC42*, *PAK1* and *WASL* in layer 3 pyramidal cells were lower by 11.3%, 15.7% and 15.0%, respectively, in subjects with schizophrenia relative to comparison subjects. In contrast, expression levels of the downstream effector molecules, such as *LIMK2* and *CDC42EP4*, were increased in layer 3 pyramidal cells in schizophrenia. For *LIMK2* mRNA, an increase of 58.9% was detected in subjects with schizophrenia. Similarly, *CDC42EP4* mRNA showed a 53.4% increase in expression in the subjects with schizophrenia.
Conclusions: Using a cell type-specific approach, our results identify several intracellular interacting partners of CDC42 with altered expression in DLPFC layer 3 pyramidal neurons in schizophrenia. These findings support the idea that altered signaling in the CDC42 pathway might contribute to the dendritic spine deficit and other morphological abnormalities in layer 3 pyramidal cells in schizophrenia. The downregulation of the principal upstream regulatory components of the CDC42 pathway could directly compromise the structural stability of dendritic spines since the CDC42-PAK interaction can modulate the polymerization of the actin cytoskeleton into filopodia, which are believed to generate mature spines. As a result, the reduced expression of the mRNAs for these proteins would be expected to be associated with a decrease in dendritic spine density. Moreover, these changes are accompanied by an apparent compensatory upregulation in the downstream effector proteins which can serve as a mechanism to enhance the stability of existing spines and promote spinogenesis in subjects with schizophrenia. Consistent with this idea, over expression of LIMK and CDC42 effector proteins (eg, CDC42EP3/4) results in suppression of actin-depolymerization activity and increased induction of pseudopodia formation, respectively. Thus, the net effect would be a promotion of actin stabilization and polymerization.
Keywords: Actin cytoskeleton, prefrontal cortex, dendritic spines, schizophrenia, CDC42
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M32. Impact of DOPA Decarboxylase Genetic Variation on Its In Vivo Enzymatic Activity in Humans

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Background: DOPA decarboxylase (DDC) is an important enzyme in the synthesis of neuroactive molecules, including dopamine, serotonin, and trace amines. Exaggerated striatal [^{18}F]-FDOPA uptake, a measure of DDC activity, has been a well replicated positron emission tomography (PET) finding in schizophrenia, interpreted to represent hallmark

illness-related presynaptic hyperdopaminergia.[1] DDC genetic variation has not only been linked to age of onset in schizophrenia,[2] but has also been implicated in risk for a range of other conditions, including attention-deficit hyperactivity disorder (ADHD),[3–5] autism,[6] suicidal behavior,[7] nicotine dependence,[8] and migraine.[9] Despite its recurrent candidacy in neuropsychiatric illness, it remains unknown whether common variation in the *DDC* gene has any impact on its product's function in vivo. In order to test the hypothesis that such genetic variation is associated with differences in [^{18}F]-FDOPA uptake, we performed both extensive single nucleotide polymorphism typing across the *DDC* gene and PET studies in a large cohort of healthy adults.

Methods: One hundred and thirteen healthy Caucasian adults (58 women, 55 men) under 55 years of age participated. Each underwent complete medical and psychiatric evaluation including history and physical examination, laboratory testing and psychiatric structured diagnostic interview to establish the absence of significant medical, substance, or psychiatric illness. Participants provided peripheral blood samples for *DDC* genotyping with Taq-Man 5'-exonuclease assay. Twenty three markers across the gene (between 15 kb upstream and 5 kb downstream) with minor allele frequencies greater than 5% and providing coverage of HapMap annotated common variants in the CEU sample (at r-squared greater than 0.8 by 2- and 3-marker tagging as implemented by *Haploview*) were genotyped. Haplotypes were generated using *PHASE* software. For PET studies, after carbidopa pretreatment to prevent peripheral tracer degradation and at least 6 h of fasting to limit tracer competition for central nervous system access, 8–16 mCi of ^{18}F-DOPA were injected intravenously and 90 min of dynamically binned images were acquired. These scans were attenuation-corrected, realigned, and coregistered to a structural MRI obtained in a separate session. Three bilateral striatal regions of interest (ROIs)—dorsal caudate, dorsal putamen, and ventral striatum (including nucleus accumbens) —were hand drawn on each individual's structural MRI and these ROIs were applied to the individual's PET scan. The Patlak-Gjedde graphical method was employed using *PMOD* software to calculate the specific uptake constant K_i using a cerebellar reference region. General linear model analyses were performed in *SPSS*.

Results: Five haplotypes with frequencies of greater than 5% were generated and were independent of age and sex (all p's > 0.1). Haplotype 1 and haplotype 4 provided nominal predictive value for ventral striatal K_i ($p = 0.023$ and 0.007, respectively) that retained significance even when controlling for sex, which, unlike age, showed an independent association with ventral striatal K_i.

Conclusions: Common variation in *DDC* predicts nominal but measureable differences in ventral striatal [^{18}F]-FDOPA uptake, suggesting a possible impact on *DDC* cis-regulation and deserving of further genetic investigation of its potential molecular underpinnings. By offering evidence for functional effects of *DDC* polymorphisms in the living human brain, this study lays groundwork upon which to pursue hypotheses linking this candidate gene and aspects of neuropsychiatric conditions with ventral striatal involvement.

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Keywords: DOPA decarboxylase, DDC, dopamine, gene, PET

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M33. Synaptophysin, vGlut1, Mitofusin2 and Calcineurin Protein Levels in the Anterior Cingulate Cortex in Schizophrenia: Relation to Treatment and Treatment Response

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Background: Schizophrenia (SZ) is a mental illness that manifests itself with psychotic symptoms, negative symptoms, and cognitive deficits. The anterior cingulate cortex (ACC) is one of several brain regions that are abnormal in SZ. Many studies show impairments in ACC function, blood flow, glutamtergic axons, pyramidal cell density and mitochondrial function. The purpose of the present study is to compare markers of synaptic density (synaptophysin) and mitochondrial fusion (mitofusin2), the vesicular glutamate transporter 1 (vGLUT1) and calcineurin in control and SZ postmortem human ACC. The SZ cohort tested as a whole and then divided by treatment or treatment response.

Methods: Postmortem human brain tissue was obtained from the Maryland Brain Collection. The number of cases in each group were: normal controls (NC) = 13; SZ = 25, treatment resistant SZ (TR) = 12, treatment responsive SZ (resp) = 13; atypical antipsychotics (aAPD) = 12 ; typical APD (tAPD) = 11. Demographics, measures of tissue quality, confounding factors were compared across groups and had no significant impact on the data. Frozen tissue from the anterior cingulatecortex from each case was used for protein analysis using Western Blot analysis. Samples were run in duplicate. Blots were probed, stripped and re-probed for actin, synaptophysin, vGlut1, calcineurin and mitofusin2. Proteins werenormalized to actin, then normalized to NC, then averaged between duplicate sets of data. Statistics were performed with SPSS and GraphPad software.

Results: Protein levels of synaptophysin, mitofusin2, vGLUT1 and calcineurin did not differ between NC and SZ group. Mitofusin was positively correlated with 1) synaptophysin in both NC ($p<0.006$) and SZ ($p<0.000$) and 2) with calcineurin in both NC ($p<0.031$) and SZ ($p<0.000$). Synaptophysin was positively correlated with 1) calcineurin only in SZ ($p<0.001$) and 2) vGlut1 ($p<0.041$) only in SZ; however the differences in correlations were not significant. In several samples the levels of vGlut1 were minuscule or absent. This pattern was not observed for any of the other proteins. Chi-square analysis showed that the proportion of NC lacking vGlut1 (1/13, 8%) was significantly different ($p<0.0001$) than that of SZ (5/25, 20%). Protein levels of synaptophysin, mitofusin2, vGLUT1 and calcineurin did not differ between NC and the SZ divided by treatment response (TR and resp). Mitofusin was positively correlated with synaptophysin in NC ($p<0.006$), TR and resp ($p<0.001$). Mitofusin was positively correlated with calcineurin in NC ($p<0.031$) and resp ($p<0.000$). Synaptophysin was positively correlated with calcineurin only in resp ($p<0.002$). This correlation was significantly higher in the resp than in the NC ($p<0.027$). Synaptophysin was positively correlated with vGlut1 ($p<0.009$) only in TR. The correlation between NC and resp was similar, but the correlation in the TR group was significantly ($p<0.031$) higher than that of the resp. Chi-square analysis showed that the proportion of NC lacking vGlut1 (1/13, 8%) was significantly different than that of TR (3/12, 25%, $p<0.0001$) and resp (2/13, 15%, $p<0.01$). The proportion of TR lacking vGlut was significantly larger ($p<0.02$ than that of resp. Protein levels of synaptophysin, mitofusin2, vGLUT1 and calcineurin did not differ between NC, and the SZ divided by APD (tAPD and aAPD). Mitofusin was positively correlated with synaptophysin in NC ($p<0.006$), tAPD and aAPD ($p<0.000$). Mitofusin was positively correlated with calcineurin in both NC ($p<0.031$) and aAPD ($p<0.000$). This correlation was similar between the NC and the tAPD, but was significantly higher in the aAPD group ($p<0.000$) than both NC or tAPD. Synaptophysin was positively correlated with calcineurin only in aAPD ($p<0.001$). This correlation was significantly higher in the aAPD group than in the NC ($p<0.017$) and compared to the tAPD group ($p<0.02$). Synaptophysin was positively correlated with vGlut1 ($p<0.012$) only in aAPD; however this correlation was not significantly different than the NC or the tAPD group. Chi-square analysis showed that the proportion of NC lacking vGlut1 (1/13, 8%) was significantly different ($p<0.001$) than that of tAPD (3/11, 27%) and the aAPD (2/12, 17%). tAPD *vs* aAPD were also significantly different ($p<0.01$) from one another

Conclusions: Synaptophysin, vGlut1, mitofusin2 and calcineurin protein levels did not differ significantly between NC and SZ, or NC and the SZ subgroups divided by treatment or treatment response status. The correlation between these proteins, which play a role in the synapse, glutamate transmission, mitochondrial fusion and calcium buffering, is complex and was differentially correlated among the groups. The proportion of subjects with a lack of vGlut1 was greater in the SZ group and the SZ subgroups than in NC.

Keywords: postmortem, neuroleptics, mitochondria, synapses, glutamate

Disclosures: R. Roberts, Nothing to Disclose; K. Barksdale, Nothing to Disclose; A. Lahti, **Part 4:** I receive medication (risperidone) from Janssen for a NIH funded study.

M34. Neurochemistry of First-Hospitalization Manic Youth

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Background: Prior research in youth with bipolar disorder has suggested that bipolar illness is associated with altered neuronal metabolism leading to neurometabolite abnormalities in multiple brain regions. These alterations include prefrontal reductions in N-acetyl aspartate (NAA) and choline (Cho), and increased levels of glutamate (glu). However, much of the research in this field is potentially confounded by the effects of repeated affective episodes, disease progression, or exposure to psychotropic medications. With these considerations in mind, we conducted an analysis of H^1 magnetic resonance spectroscopy (MRS) data examining neurometabolite levels in the ventrolateral prefrontal cortex and anterior cingulate cortex of youth with bipolar disorder early in their illness course. We expected that bipolar youth would exhibit abnormalities in neurometabolite levels relative to typically developing youth. In particular, we hypothesized that youth with bipolar disorder would have elevated levels of glutamate and decreased levels of NAA and choline.

Methods: Adolescents ages 10–17 years 11 months with bipolar disorder type I were recruited from inpatient units during their first manic or mixed episode. Diagnosis of bipolar disorder was confirmed using the Washington University in St. Louis Kiddie-Schedule for Affective Disorders and Schizophrenia (WASH-U KSADS), and all bipolar adolescents had a baseline Young Mania Rating Scale (YMRS) score $\geqslant 20$. All participants with bipolar disorder were less than 2 years from onset of their first DSM-IV-TR affective episode, had no prior psychiatric hospitalizations, and had $<$ 3 months of lifetime psychotropic medication exposure (not including stimulants). A comparison group of typically developing adolescents was also recruited. All subjects completed a high resolution structural scan and H^1 MRS scans, with separate 8cc voxels placed in the right and left ventrolateral prefrontal cortex and the anterior cingulate cortex. All subjects were scanned using a 4.0 Tesla Varian Unity INOVA MRI scanner. Tissue segmentation for each voxel was performed on the structural scans using statistical parametic mapping (SPM). Metabolite levels for myo-inositol (mI), NAA, Cho, creatine (Cr) and glu were determined using the Linear Combinations of model spectra (LCModel) software. Metabolites other than glu were corrected for the tissue content of the voxel and scan parameters. Initial analysis focused on group differences, and comparisons of demographic variables and metabolite levels were conducted in SAS using t-tests for continuous variables and chi-square tests for categorical variables. Secondary analyses looked for

differences between metabolite levels between girls and boys and relationships between metabolite levels and age.
Results: Seventy-one adolescents with bipolar disorder and 39 healthy adolescents participated in this study. Of the adolescents with bipolar disorder, 30 (42%) were boys, 49 (69%) were white, and the mean (SD) age 14.3 (1.8). Nineteen (49%) of the healthy adolescents were boys, 22 (56%) were white, and the mean (SD) age was 14.7 (1.7). There were no significant differences between the groups in any of these demographic variables. There were no significant differences between youth with early-course bipolar disorder and typically developing youth in any of the neurometabolites considered. There were also no significant correlations between any of the metabolites considered and age. When the group analysis was repeated using age as a covariate, there were no significant group effects and no group by age interactions. The levels of several metabolites differed significantly between boys and girls. In the ventrolateral prefrontal cortex, boys had significantly higher levels of mI, NAA and Ch2 on the right, and higher levels of all metabolites on the left. In the anterior cingulate cortex, only the levels of mI differed significantly, again with boys having higher levels than girls. However, there was no difference in this pattern between youth with bipolar disorder and healthy youth. When the group analysis was repeated using sex as a covariate, there were still no significant effects of diagnosis, and no interactions between diagnosis and sex.
Conclusions: Our results suggest that mania early in the course of bipolar disorder is not associated with alterations in neurometabolite levels in the ventrolateral prefrontal cortex or the anterior cingulate cortex. These results are consistent with the only other study of first episode manic youth, a smaller sample that was then treated with olanzapine. Such alterations, previously detected in samples not confined to first-episode patients, may be a result of disease progression or the effects of medication, but not present at the onset of bipolar illness. Indeed, several studies have found that the treatment of manic youth with medications, including divalproex, quietapine, and lithium, leads to changes in neurometabolite levels. The presence of significant sex effects in the levels many of the neurometabolites makes it clear that future studies should carefully consider including sex in models of neurometabolite data, even in the absence of group differences in sex ratio. Further research is in progress which will expand upon the sample described here and explore the effect of pharmacological treatments on these neurometabolite levels.
Keywords: bipolar disorder, adolescents, MRS, neurometabolites, sex
Disclosures: M. Schneider, Nothing to Disclose; T. Benanzer, Nothing to Disclose; W. Weber, Nothing to Disclose; L. Patino Duran, Nothing to Disclose; J. Strawn, Nothing to Disclose; J. Welge, Nothing to Disclose; C. Adler, Nothing to Disclose; S. Stephen, Nothing to Disclose; M. DelBello, Nothing to Disclose.

M35. Cortical Thickness in Individuals with Subclinical and Clinical Psychotic Symptoms

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Background: Symptoms that are linked to schizophrenia and other psychotic disorders, such as auditory verbal hallucinations, are also commonly reported by individuals who function well in society, are not in need for care and do not suffer from schizophrenia or another psychotic disorders. These individuals provide the opportunity to investigate the relationship between subclinical psychotic symptoms and brain morphology unaffected by (antipsychotic) medication. The purpose of this study was to compare cortical thickness in non-psychotic individuals with auditory verbal hallucinations to healthy subjects and to patients with schizophrenia spectrum disorders.
Methods: Fifty healthy subjects, 50 non-clinical individuals with auditory verbal hallucinations (AVH group) and 50 patients with a schizophrenia-spectrum disorders participated in the study and underwent structural magnetic resonance imaging. The three groups were matched for age, gender, handedness and years of parental education. Cortical thickness was assessed using the FreeSurfer software suite.
Results: Patients with schizophrenia spectrum disorders showed reduced cortical thickness in widespread frontal, temporal, and parietal areas compared to both other groups. The AVH group showed cortical thinning in the left paracentral gyrus, right insula, right fusiform gyrus, right inferior temporal gyrus and the left pars orbitalis compared to the healthy subjects. Additional analyses revealed that for a large majority of cortical brain structures (88%), the healthy subjects had the highest cortical thickness, the patients had the lowest thickness, while the AVH individuals showed values that were in between these two groups.
Conclusions: Individuals with auditory hallucinations in the absence of other psychotic symptoms and who function well and are unmedicated show a similar but less pronounced pattern of structural brain differences as patients with schizophrenia spectrum disorders, suggesting that cortical thinning is associated with the propensity for, or presence of, auditory verbal hallucinations.
Keywords: schizophrenia, non-clinical psychotic symptoms, cortical thickness, spectrum
Disclosures: I. Sommer, Nothing to Disclose; M. Begemann, Nothing to Disclose; R. van Lutterveld, Nothing to Disclose.

M36. Brain Activation to Natural Cues and Drug Cues and Dopamine Receptors in Cocaine Addicts

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Background: Mechanisms of natural reward in the mesolimbic DA pathway reinforce the behaviors that are necessary for survival. It has been postulated that cocaine-induced neuroadaptations hijack the dopaminergic pathways of natural reward, gradually impairing, learning and memory, executive function and self-control as a function of drug exposure. However, the overlap of the networks of natural and drug rewards and the role of dopamine (DA) in these networks are largely unknown. PET and fMRI studies have shown that drug addiction impairs the limbic system

and regions involved in attention, memory, salience, motivation, executive function, mood and interoception. Like drugs, foods increase striatal DA release and are potently rewarding. Differently, food intake is determined not just by the pleasure of eating but also by the balance of energy and nutrients in the body. Thus we hypothesized that cocaine cues and food cues would activate brain networks that will show significant overlap and also differential patterns

Methods: We evaluated DA D2/D3 receptors in the striatum and whole-brain activation in 20 cocaine-abusing males that were 46.4 ± 3.3 years old and had body mass index (BMI) of $26 \pm 4\,kg/m^2$, smoked 3.2 ± 2.3 mg of cocaine and expended 136 ± 94 dollars in cocaine per day during the last 17.9 ± 7 years. All subjects had a positive urine toxicology screen for cocaine on screening days, indicating that they have used cocaine during the prior 72 h, but their urines were negative on scanning days. We used two blocked fMRI tasks contrasting neutral- vs. cocaine-cue video epochs, and neutral- vs. food-cue video epochs. Single-shot EPI scanning was used to record the fMRI responses to neutral, cocaine and food cues in a 4-Tesla MRI scanner. Immediately after fMRI scanning the subjects underwent PET in a HR+ tomograph with [^{11}C]raclopride, a radiotracer that binds to DA D2 and D3 receptors (D2R). Standard imaging preprocessing and statistical analyses in SPM8 were used to analyze the fMRI and PET datasets. One-way within-subjects ANOVA was used to test for common and differential activation patterns to neutral, cocaine and food cues. Voxelwise multiple regression analyses were used to assess the association between D2R levels in the striatum and fMRI responses across subjects. Statistical significance was set as $P_{FWE} < 0.05$, corrected for multiple comparisons.

Results: Compared to neutral cues, cocaine cues produced fMRI responses in cerebellum, caudate and nucleus accumbens (NAc), and food cues produced fMRI responses in somatosensory and gustatory cortices, insula, anterior thalamus and hypothalamus. Together, cocaine and food cues produced higher activation than neutral cues in cerebellum, PFC, OFC and insula, and higher deactivation in NAc and hypothalamus, ACC and default-mode network (DMN) regions. Food cues produced higher activation than cocaine cues in superior temporal, inferior frontal cortex and insula, and higher deactivation in DMN. Increased D2R in the striatum was associated with stronger fMRI responses in somatosensory and gustatory cortices, hippocampus and DMN, and weaker responses in cerebellum, premotor cortex, ACC and OFC. Longer cocaine exposure was associated with lower activation in cerebellum. The fMRI responses to cocaine and food cues in somatosensory cortex, cerebellum and DMN increased in proportion to how much the subjects liked the cues and to their BMI.

Conclusions: The current study demonstrates for the first time common and distinct functional circuits involved in drug (cocaine cues) and natural (food cues) reward for men that actively abuse cocaine. Compared to neutral cues, cocaine and food cues increased activation in a common network that includes cerebellum, anterior insula, OFC, and inferior frontal and parietal cortices, as well as increased deactivation in NAc and DMN regions. Stronger co-deactivation to cocaine and food cues than to neutral cues in the NAc is consistent with the inhibitory properties of DA in the striatum of primates and with the fact that all addictive drugs increase DA in NAc, and their behavioral rewarding effects are associated with increases in synaptic DA in NAc. Brain activation in posterior insula, and inferior frontal cortex and deactivation in posterior DMN regions were higher for food cues than for cocaine cues. Brain activation in these networks showed significant correlation with the availability of DA D2/D3 receptors in the striatum, year of cocaine use, BMI and with the behavioral responses (liking scores) to food and cocaine cues, suggesting that cocaine hijacks natural reward/motivation pathways as a function of drug exposure.

Keywords: Addiction, fMRI, cocaine, PET, dopamine

Disclosures: D. Tomasi, Nothing to Disclose; G. Wang, Nothing to Disclose; E. Caparelli, Nothing to Disclose; N. Volkow, Nothing to Disclose.

M37. Brain-derived Neurotrophic Factor and Deficient Amygdala Habituation in Borderline Personality Disorder: A Research Domain Criteria Imaging Genetics Study

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Background: Borderline personality disorder (BPD) is characterized by hyperarousal, a Research Domain Criteria [RDoC] construct. Biomarkers of hyperarousal including amygdala hyper-reactivity and deficient amygdala habituation to repeated emotional stimuli are putative endophenotypes of BPD. The Met allele of the Val66Met SNP of the brain-derived neurotrophic factor gene (BDNF) increases amygdala reactivity and impairs extinction learning, a phenomenon closely related to habituation.

Methods: We used an imaging genetics framework to examine for the first time in BPD patients the impact of BDNF Val66Met genotypes on amygdala habituation to repeated emotional and neutral pictures. We employed event-related functional magnetic resonance imaging (fMRI) in unmedicated BPD ($n = 33$) and schizotypal personality disorder (SPD, $n = 28$) patients and healthy controls (HC, $n = 32$) during a task involving viewing unpleasant, neutral, and pleasant pictures presented twice. Amygdala responses were examined with a mixed-model multivariate ANOVA including BDNF Val66Met SNP genotype (Met-carriers vs. Non-Met carriers). Specifically, we conducted a diagnostic group (HC vs. BPD vs. SPD) $\times$ genotype (Met-carriers *vs* Non-Met carriers) $\times$ picture type (U, N, P) $\times$ picture repetition (novel, repeated) $\times$ startle stimulus (startle presented 4,000 msec following picture onset, no startle stimulus) $\times$ hemisphere (left, right) $\times$ time (1 to 11: 3 s, 6, 9...33 s following picture onset) multivariate analysis of variance.

Results: A significant Diagnostic group $\times$ Genotype (BDNF Val66Met SNP Met- vs. Non-Met-carriers) $\times$ Picture type (unpleasant, neutral, pleasant) $\times$ Picture repetition (Novel/Repeat) $\times$ Time interaction indicated that Met-carrying BPD patients (but not Met-carrying SPD patients or HCs) showed exaggerated amygdala reactivity to repeated, but

not novel, unpleasant pictures, representing a failure to habituate.
Conclusions: Using an imaging-genetics approach we characterize for the first time the genetic underpinnings of the deficit in amygdala habituation to emotional stimuli in BPD, which is restricted to those carrying the BDNF 66Met allele. This important finding points to BDNF modulators as a novel therapeutic avenue for BPD, a disorder which lacks FDA-approved medications.
Keywords: BDNF, amygdala, habituation, borderline personality disorder, emotion regulation
Disclosures: M. Perez-Rodriguez, Nothing to Disclose; A. New, Nothing to Disclose; K. Goldstein, Nothing to Disclose; Q. Yuan, Nothing to Disclose; Z. Zhou, Nothing to Disclose; C. Hodgkinson, Nothing to Disclose; D. Goldman, Nothing to Disclose; L. Siever, Nothing to Disclose; E. Hazlett, Nothing to Disclose.

M38. The Spatiotempotal Organization of Subcortical Anatomy in Human Development

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Background: Access to large-scale longitudinal structural neuroimaging data has fundamentally altered our understanding of cortical maturation and organization en route to human adulthood, with consequences for basic science, medicine and law. In striking contrast to the rapid accrual and refinement of cortical insights, basic anatomical development of subcortical structures such as the basal ganglia and thalamus still remains very poorly described—despite the fact that these evolutionarily ancient structures are intimate working partners of the cortical sheet and critical to diverse developmentally emergent skills and disorders.
Methods: Here, we address this disparity by applying novel methods for analysis of subcortical volume and shape to over 1171 structural magnetic resonance imaging brain scans from 618 typically developing males and females aged 5 to 25 years.
Results: We find that the human striatum, pallidum and thalamus each follow a distinct 'inverted-U' trajectory of volume change. These trajectories show a relative delayed in males, and peak later than the trajectory of cortical volume change in both sexes. Changes in global subcortical volume hide profound regional heterochronicity: prefrontally-connected striatal, pallidal and thalamic facets form islands of areal contraction within an otherwise generalized surface area expansion with age. We also identify hotspots of sexually dimorphic shape change in each of the three structures examined—with relevance for sex-biased mental disorders emerging in youth. Finally, by blending structural covariance analysis with genomic methods for module detection, we create an entirely data-driven parcellation of the subcortical surface for wider use. The macroscopic organization captured by this parcellation respects microscopic distinctions engrained within our histology-based method for image analysis.
Conclusions: These data provide a spatiotemporal model of the human subcortex that is comparable in detail to models that have long been available for the cortex—setting the stage for a more holistic consideration of developmental processes sculpting the human brain through childhood, adolescence and early adulthood.
Keywords: Development, MRI, subcortex, WGCNA
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M39. Parametric Modulation of Neural Activity during Face Emotion Processing in Unaffected Youth at Familial Risk for Bipolar Disorder

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Background: Deficits in face emotion processing have been proposed as a candidate endophenotype for bipolar disorder (BD). Face labeling deficits are present in BD patients regardless of mood state, psychotropic medication, or comorbidity status. Moreover, impairments are found in unaffected children at familial risk (Brotman *et al*. 2008). Meta-analyses in BD suggest limbic hyperactivation and prefrontal cortex (PFC) hypoactivation during face emotion paradigms (Delvecchio *et al*. 2012; Houenou *et al*. 2011). Most recently, work has demonstrated similar dysfunction in the neural circuitry mediating face processing in both pediatric BD patients and youth at familial risk (Olsavsky *et al*. 2012). Consistent with this, amygdala and prefrontal cortex dysfunction have been suggested as pathophysiological risk markers for BD (Ladouceur *et al*. 2013; Roberts *et al*. 2013). Few studies, however, have examined the neural correlates to subtle changes in emotional expressions in BD youth. In one study, relative to healthy comparison youth, BD patients failed to modulate the amygdala and frontal cortex in response to increasing anger intensity on the face (Thomas *et al*. 2012). Research has yet to examine neural responsiveness to subtle changes in face emotion in youth at familial risk. In this study, we compare neural activation in pediatric BD, youth at familial risk, and age-matched healthy comparison children on a parametrically designed face emotion processing task. Behaviorally, we anticipated that pediatric BD and at risk youth would demonstrate abnormal face emotion ratings. In addition, we hypothesized that, in response to increasing anger on the face, both BD and youth at risk would exhibit similar abnormal linear trends in the amygdala and prefrontal cortex compared to healthy youth.
Methods: Functional magnetic resonance imaging (fMRI) data were acquired from 64 participants (8–18 years old), including 20 pediatric BD patients, 15 unaffected children at familial risk, and 29 healthy comparison youth. At risk children had at least one first-degree (parent and/or sibling) BD relative. At risk children with a mood disorder were excluded from the study; youth with ADHD or an anxiety

disorder were included. Angry and happy faces with increasing emotion intensity [0% (neutral), 25%, 50%, 75%, and 100%] were presented during two rating conditions. Participants made either explicit ('How hostile is the face?') or implicit ('How wide is the nose?') ratings on 1–5 scale (1 = least hostile/wide; 5 = most hostile/wide). In this abstract, we focus on data from the angry face condition. Group x rating condition x intensity level repeated measures ANOVAs were performed on rating and reaction time data. Linear trends between neural activation and increasing emotional intensity were explored using amygdala region of interest and whole-brain analyses ($p < 0.005$; $k > 10$) (Lieberman and Cunningham, 2009).

Results: Groups did not differ on age, IQ, or sex distribution. There was a significant group x rating condition interaction [$F(2, 244) = 3.54$, $p = 0.035$], with BD ($p = 0.001$) and at risk ($p = 0.05$) rating faces as less hostile than healthy comparison youth. There were no differences in reaction time across groups. Linear trend analyses in both the left and right amygdala revealed a main effect of group [left ($p = 0.002$); right ($p = 0.007$)]. With increasing anger on the face, healthy comparison youth showed a more marked increase in amygdala activation than either BD ($p < 0.05$) or at risk ($p < 0.01$). From the whole-brain analysis, there were two clusters showing a significant group x rating condition interaction: inferior frontal gyrus (IFG, BA 46) and anterior cingulate cortex (ACC, BA 25). During hostility ratings, both BD ($p < 0.05$) and at risk ($p < 0.01$) youth demonstrate decreased IFG modulation relative to healthy comparison youth. In the ACC, BD showed *increased* modulation was during hostility ratings relative to both at risk ($p < 0.01$) and healthy comparison youth ($p < 0.05$), and *decreased* modulation during nose width ratings relative to healthy comparison youth ($p < 0.01$).

Conclusions: Similar to previous behavioral results, both BD and at risk youth demonstrated abnormal face emotion ratings (Brotman *et al*. 2008). Consistent with prior work showing amygdala and PFC dysfunction (Ladouceur *et al*. 2013; Olsavsky *et al*. 2012; Roberts *et al*. 2013; Surguladze *et al*. 2010), both BD and unaffected relatives showed reduced modulation of the amygdala and IFG. Dysfunctional modulation of the amygdala and IFG in BD and youth at risk may be a candidate pathophysiological endophenotypic marker for BD, and may underlie social cognition and face emotion labeling deficits seen in BD and at risk youth. Work is needed to examine the relationship between amygdala hyperactivity and PFC hypoactivity and dysfunctional modulation. Future studies should include larger samples and a longitudinal design to determine whether the neural deficits associated with face processing 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

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M40. Non-smoking Chronic Alcoholics Following Withdrawal Show Increased Cerebral Blood Flow and Altered Brain Docosahexaenoic (DHA) Metabolism on Partial Volume Error-corrected PET

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Background: Chronic alcohol dependence has been associated with disturbed behavior, brain atrophy and a low plasma concentration of the polyunsaturated fatty acid (PUFA), docosahexaenoic acid (DHA, 22:6n-3), particularly if liver disease is present. In addition, 33Xe clearance, SPECT (single photon emission computed tomography) and PET (positron emission tomography) imaging studies have reported that regional cerebral blood flow (rCBF) or that the cerebral metabolic rate for glucose (rCMRglc) is decreased in chronic alcoholics after withdrawal. In animal models, excessive alcohol consumption is reported to reduce brain DHA concentration, suggesting disturbed brain DHA metabolism. We hypothesized that brain DHA metabolism also is abnormal in chronic alcoholics, and that changes in brain DHA metabolism in alcoholics compared with controls would be accompanied by changes in rCBF.

Methods: Under an NIAAA IRB approved protocol, we compared 15 non-smoking chronic alcoholics, age 44 ± 14 (SD) years, within 7 (4.8 ± 1.1) days of their last drink, with 22 non-smoking healthy controls (age 36 ± 14 years). Age of onset of heavy drinking in the alcoholics was 26.9 ± 10.6 years. We used our published neuroimaging PET method [1] to measure regional coefficients (K^*) and rates (J_{in}, K^* x unesterified plasma DHA concentration) of incorporation of unesterified DHA from plasma into brain of chronic alcoholics and controls, using [1-^{11}C]DHA. Plasma unesterified DHA concentration also was quantified. We first measured rCBF with [^{15}O]water in the same PET session, since its radioactive half-life is only 2 min and it does not interfere with DHA measurement. PET data were partial volume error (PVE)-corrected for brain atrophy. PUFA brain incorporation parameters K^* and J_{in} have been shown to be unaffected by changes in rCBF, so that we could assess brain DHA incorporation and flow as independent measures of DHA metabolism and functional activity, respectively. DHA incorporation is an estimate of net metabolic loss, since evidence indicates little DHA synthesis from n-3 PUFA precursors in mammalian brain, thus that brain DHA largely is derived from blood.

Results: PVE-corrected K^* for DHA was significantly and widely elevated throughout the brain by 10–20%, and PVE-corrected rCBF was elevated by 7%-34%, in the alcoholics compared with controls. Unesterified plasma DHA did not differ significantly between the groups, although it was insignificantly low, nor did whole brain J_{in}, the product of K^* and plasma DHA concentration.

Conclusions: The significant elevations in the chronic alcoholics of PVE-corrected K^* for DHA indicate increased brain avidity for DHA (for replacing DHA that is metabolically consumed), thus a brain DHA metabolic deficit vis-à-vis plasma DHA availability. Higher rCBF in alcoholics also suggests increased energy consumption.

Each of these changes may reflect a hypermetabolic state related to alcohol withdrawal, or a general brain metabolic change in chronic alcoholics independently of withdrawal. Our finding elevated rCBF in chronic alcoholics, in contrast to the many reported reductions in rCBF or rCMRglc, may have been due to (a) our using quantitative PVE-corrected PET, compared 33Xe clearance, SPECT or non-PVE corrected PET in the prior studies, and (b) our studying non-smoking patients and controls (as smoking can modify rCBF). Ref: [1]. Umhau *et al*. (2009) Imaging incorporation of circulating docosahexaenoic acid into the human brain using positron emission tomography. J. Lipid Research 50: 1259–1268.

Keywords: chronic alcoholism, positron emission tomography, cerebral blood flow, docosahexaenoic acid, brain

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M41. Developmental Differences in Resting-state Network Connectivity in Autism Spectrum Disorder

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Background: Autism Spectrum Disorder (ASD) has been associated with a complex pattern of increases and decreases in resting-state functional connectivity. The developmental disconnection hypothesis of ASD poses that shorter connections become overly well established with development in this disorder, at the cost of long-range connections. Many resting-state networks can already be identified in young children, but they are under developmental influences. Here, we investigated resting-state connectivity in relatively young boys with ASD and typically developing children. We hypothesized that ASD would be associated with reduced connectivity between networks, and increased connectivity within networks, in line with the developmental disconnection hypothesis.

Methods: We acquired resting-state fMRI from 27 boys with ASD and 29 age-matched typically developing boys between 6 and 16 years of age. Using independent component analysis, we identified 14 resting-state networks of interest. Group differences for within- and between network connectivity were tested using 5000 Monte-Carlo permutation tests, with age as covariate. Permutation tests were also performed in a sub-group of 24 individuals with Autism Spectrum Disorder to test for correlations with scores on the Repetitive Behavior Scale-revised (RSB-R). Results were FWE-corrected for multiple comparisons, using threshold-free cluster enhancement.

Results: We found no between-group differences in within-network connectivity. However, we did find reduced functional connectivity between two higher-order cognitive networks in ASD. Furthermore, we found that increased connectivity within the default mode network correlated with age in ASD, whereas it did not in typically developing children. In 24 children with Autism Spectrum Disorder, RBS-R scores were positively correlated with increased connectivity within a cerebellar and executive network. Post-hoc analyses showed the highest correlations for insistence on sameness and ritualistic behavior.

Conclusions: Our results suggest that the global architecture of functional networks is intact in ASD, as many major networks can already be detected in relatively young boys with ASD. However, there are subtle differences in between-network connectivity, as well as subtle developmental changes. These findings are in line with developmental disconnection hypothesis of ASD, as the differences are mostly found in between-network connectivity. Furthermore, this may be related to behavioral symptoms for children and adolescents with Autism Spectrum Disorder, as severity of restricted and repetitive behavior was related to -state connectivity in a cerebellar and executive network.

Keywords: ASD; RS-fMRI; development; Repetitive behavior

Disclosures: D. Bos, Nothing to Disclose; T. van Raalten, Nothing to Disclose; A. Smits, Nothing to Disclose; J. van Belle, Nothing to Disclose; S. Rombouts, Nothing to Disclose; S. Durston, Nothing to Disclose.

M42. Abnormal Functional Brain Network Organization for Visual Processing of Non-appearance Stimuli in Body Dysmorphic Disorder

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Background: Body dysmorphic disorder (BDD) is characterized by preoccupation with misperceived defects of appearance, causing significant distress and disability. Despite its prevalence (1–2% of the population) and severity, little is known about the neurobiology. Previous functional magnetic resonance imaging (fMRI), neurocognitive, and psychophysical studies in BDD suggest abnormalities in information processing characterized by greater local relative to global processing for appearance-related and non-appearance related stimuli. Recent white matter structural analyses have found abnormal network organization and abnormal connectivity patterns. However, to date there have been no studies of functional brain connectivity in BDD. The purpose of this study is to investigate functional brain connectivity in the visual system related to processing of non-appearance related stimuli in individuals with BDD compared to healthy controls. We used partial correlation analysis and graph theory to provide a quantitative assessment of functional brain network organization in the visual system during a visual processing task. Based on findings from a previous structural network analysis, we hypothesized that individuals with BDD would have greater mean clustering coefficient, abnormal edge betweenness centrality between occipital poles, and lower node degree and betweenness centrality of dorsal visual stream regions (cuneus and lateral occipital cortex,

superior). Based on previous studies, we also hypothesized lower node degree in lower- and higher-order visual processing regions including the intracalcarine cortex, lingual gyrus, temporal occipital fusiform cortex, temporal fusiform cortex, parahippocampal gyrus, cuneus, and precuneus.
Methods: Participants: 31 medication-free, right-handed males and females with DSM-IV BDD ($N=15$), and healthy controls ($N=16$) of equivalent gender, age, and years of education participated. MRI: participants underwent scanning with fMRI on a 3-T (Siemens) scanner while performing a matching task of photographs of houses. We acquired BOLD contrast images using a T2*-weighted echo planar imaging (TR = 2.5 s, TE = 35 ms, flip angle = 90°, matrix = 64x64, field of view = 24x24 cm, in-plane voxel size 3.1x3.1 mm, slice thickness 3 mm, 1 mm gap, 28 slices). We acquired high-resolution structural MRI brain scans (T1-weighted MPRAGE, sagittal, 1x1x1 mm voxels) for each participant. FSL provided the tools for preprocessing, registration, and analysis. Anatomical nodes in the visual system (22) were selected using the Harvard Oxford cortical and subcortical atlas. We regressed out motion parameters, and white matter and CSF activation, but not global signal. Activation time series for each node, averaged across voxels, were used to create a 22x22 partial correlation weighted connectivity matrix. We normalized the sparsity level of the matrices by thresholding at top 50% of connection strengths, then we derived the graph theory metrics of interest, using the Brain Connectivity Toolbox (www.brain-connectivity-toolbox.net) implemented in Matlab. Statistical Analysis: we used unpaired t-tests to test group differences related to our hypotheses ($\alpha > 0.05$, one-sided, Bonferroni corrected). We conducted exploratory analyses across all nodes, of node degree, betweenness centrality, clustering coefficient, and regional efficiency ($\alpha > 0.05$, two-sided, FDR corrected).
Results: We found significantly greater mean clustering coefficient in controls relative to BDD participants ($p = 0.03$), contrary to our hypothesis. As hypothesized, there were lower node degrees in dorsal visual stream nodes, including the left cuneus and the left superior lateral occipital cortex. There was no abnormality in edge betweenness centrality between the right and left occipital poles. In addition, as part of an exploratory analysis, we found significantly lower node betweenness centrality in the left inferior lateral occipital cortex, and greater local efficiency in the left precuneous. (All $p < 0.05$ for nodal comparisons.)
Conclusions: This is the first study to investigate functional network connectivity using graph theory metrics in individuals with BDD. We found abnormalities in BDD for specific nodes critically important in visual processing, as well as global abnormalities in clustering coefficient. These results, combined with recent findings of abnormalities in structural connectivity, suggest a pattern of aberrant functional integration as well as structural network abnormalies in BDD. Such abnormalities in functional connectivity in visual systems may have implications in understanding perceptual disturbances in this disorder.
Keywords: body dysmorphic disorder, network analysis, fMRI, graph theory, functional connectivity
Disclosures: T. Moody, Nothing to Disclose; J. Brown, Nothing to Disclose; A. Leow, **Part 2:** I have received compensation, in excess of 10k per year since 2010, through clinical work as an outpatient psychiatrist from community psychiatry in California.; L. Zhan, Nothing to Disclose; J. Feusner, Nothing to Disclose.

M43. Reward-based Spatial Learning in Unmedicated Adults with Obsessive-Compulsive Disorder

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Background: Structural and functional abnormalities in fronto-striatal circuits involving orbitofrontal cortex and ventral striatum are reported in OCD. These ventral fronto-striatal and connected mesolimbic regions (hippocampus and amygdala) are involved in reward processing functions that may be impaired in persons with OCD, contributing to, for example, their feeling that 'something is wrong' when experiencing obsessions. The hippocampus along with other medial temporal lobe structures, is also involved in spatial navigation and learning. Thus, we used a novel, translational fMRI task to examine the functioning of the neural circuits that support reward-based spatial learning in unmedicated adults with Obsessive-Compulsive Disorder (OCD). This task is a directly analogous to the radial arm maze experiments used to define the neuroanatomical and neurochemical bases of learning systems in rodents (e.g., Packard *et al*, *J Neurosci*, 1989) carefully tailored to a human virtual reality environment within the MRI scanner.
Methods: We compared fMRI BOLD response in 33 adults with OCD to 33 healthy, age-matched control (HC) participants during performance of a reward-based learning task that required learning to use extra maze cues to navigate a virtual 8-arm radial maze to find hidden rewards. We used general linear modeling to compare groups in their patterns of brain activation associated with reward processing during spatial learning ('learning condition') versus a control condition in which rewards were unexpected because they were allotted pseudo randomly; thus, spatial learning (i.e., using the cues to navigate and find rewards) was experimentally prevented.
Results: Behavioral performance on the task did not differ between groups and both groups activated temporoparietal during spatial navigation in the learning condition. However, only OCD participants activated left hippocampus during navigation and in response to receiving expected rewards in that condition. In contrast, activation of left hippocampus and amygdala in HC participants was associated with receiving unexpected rewards in the control condition. Activation of bilateral ventral striatum in HC participants was associated with not receiving expected rewards in the learning condition, and the OCD participants with the most severe symptoms activated bilateral ventral striatum the least during this condition. Left amygdala activation was associated with the anticipation of rewards in the learning condition in OCD group, but in the control condition in the HC group.

Conclusions: When processing rewards on a translational reward-based learning fMRI task, OCD participants displayed aberrant recruitment of mesolimbic areas (amygdala and hippocampus) and ventral striatum. Consistent with our previous findings from a separate sample of healthy individuals (Marsh *et al*, *Neuropsychologia*, 2010), HC participants activated this system in response to the violation of reward expectations during task performance. These findings are also consistent with neurophysiological findings from rodents, showing that dopaminergic midbrain neurons fire in response to unpredicted rewards. In contrast to the HC group, unmedicated OCD participants activated left amygdala when anticipating and left hippocampus when processing expected rather than unexpected rewards. These findings suggest that the dopaminergic innervation of this circuit during reward processing may be dysfunctional in OCD, and suggest that future studies could use the radial-arm maze paradigm to manipulate and probe the functioning of this circuit in animal models of OCD.

Keywords: Obsessive-Compulsive Disorder, fMRI, reward, learning, translational

Disclosures: R. Marsh, Nothing to Disclose; Y. Huo, Nothing to Disclose; G. Lui, Nothing to Disclose; M. Packard, Nothing to Disclose; G. Tau, Nothing to Disclose; X. Hao, Nothing to Disclose; B. Peterson, Nothing to Disclose; Z. Wang, Nothing to Disclose; H. Simpson, Nothing to Disclose.

M44. Alterations of Cortical Thickness Related to Clinical Severity, but not the Untreated Disease Duration in Schizophrenia

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Background: Though previous studies have reported deficits in the grey matter volume of schizophrenia patients, it remains unclear whether these deficits occur at the onset of the disease before treatment and whether they are progressive over the untreated disease duration. Furthermore, the grey matter volume of a cortical region represents the combination of its cortical thickness and the surface area; these features are believed to be influenced by different genetic factors. However, the cortical thickness in the first episode of drug-naïve schizophrenia has seldom been investigated. Thus, the present study aimed to investigate cortical thickness differences in a large sample of 128 first-episode drug-naïve schizophrenia patients and 128 healthy controls. We hypothesised that 1) regional reductions in cortical thickness would be observed in early stages of schizophrenia and 2) changes in cortical thickness would be related to the clinical severity as well as the untreated duration of the disease.

Methods: This study was approved by the local ethical committee and written informed consent was obtained from all subjects. One hundred twenty-eight antipsychotic-naïve first-episode schizophrenia patients (78 females, mean age 24.3 ± 8.1 years) and 128 healthy comparison subjects (65 females, mean age 26.1 ± 8.3 years) 128 antipsychotic naïve first episode schizophrenia patients were recruited and were performed MR examination via a 3-Telsa GE MRI system. We employed CIVET software (version 1.1.9, Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada) to extract cortical thickness measurements from T1weighted MRI images. Vertex-based 2-sample ttest was applied to investigate cortical thickness differences between the patient group and the healthy control group with age and sex as covariance. Statistical significance was set at $p<0.05$ with false discovery rate correction for multiple comparisons. Global Assessment of Functioning Scale (GAF) and Positive and Negative Syndrome Scale (PANSS) were used to assess the neuropsychological functioning and clinical symptoms of schizophrenia patients. Besides, correlation analysis between significant differences of cortical thickness in patient group and scale scores was performed to reveal the potential association between the anatomical deficits and clinical symptoms.

Results: Compared to controls, patients exhibited significantly reduced cortical thickness primarily in the right dorsolateral prefrontal cortex (DLPFC), left precentral gyrus, left orbitofrontal cortex (OFC), left inferior frontal gyrus pars triangularis and right precentral and postcentral gyri ($p<0.05$, corrected for multiple comparisons). In addition, significant cortical thickening was found in the bilateral anterior temporal lobes and the left medial orbitofrontal cortex (med-OFC) and left cuneus in patients compared to controls ($p<0.05$, corrected for multiple comparisons). The average cortical thickness of the regions with reduced cortical thickness, i.e., right DLPFC, bilateral precentral gyri, left OFC and left inferior frontal gyrus pars triangularis, was negatively correlated with symptom severity, as identified by the PANSS scores. However, no significant correlation was observed between the cortical thickness in each region with altered thickness and the untreated duration of illness ($p>0.05$). Furthermore, patients with shorter untreated durations of illness (<12 months, 81 cases) exhibited no significant differences compared to patients with longer untreated illness durations ($\geqslant 12$ months, 37 cases) ($p>0.05$).

Conclusions: The current study provided the first empirical evidence of widespread deficits in cortical thickness, including both thinning and thickening, in the largest sample of antipsychotic-naïve first-episode schizophrenia patients to date. Furthermore, these anatomical changes were related to the clinical symptoms observed in schizophrenia but not to the untreated illness duration. This finding suggests that these anatomical deficits may be associated with aberrant neurodevelopmental processes and may be relatively stable in very early stages of the disease. However, it remains unclear whether these deficits are progressive in patients with longer untreated courses of schizophrenia. Further study of antipsychotic-naïve patients with longer untreated illness courses may help clarify the effect of illness course on the brain in the later stages of disease as well as the natural dynamic of disease progression in schizophrenia.

Keywords: Neuro-Imaging, Magnetic resonance imaging, Schizophrenia, Cortical thickness, Brain structures.

Disclosures: S. Lui, Nothing to Disclose; Y. Xiao, Nothing to Disclose; L. Yao, Nothing to Disclose; Y. He, Nothing to Disclose; Q. Gong, Nothing to Disclose.

M45. Differential Effects of Estrogen Hormone Therapy on CA1 Hippocampal Subfield Volume Change over a 2-Year Observation Period in Postmenopausal Women at Risk for Alzheimer's Disease: Conjugated Equine Estrogen Versus Estradiol

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Background: Significant controversy surrounds the use of estrogen-based hormone therapy (HT) among postmenopausal women and associated effects on the brain and risk of cognitive decline. Many studies have found larger hippocampal volumes among postmenopausal women using estrogen HT compared to women naïve to or non-users of HT, while others have reported no differences among HT users. These investigations are limited by cross-sectional evaluations and heterogeneity of sample characteristics and types of estrogen preparations. There is strong evidence of differential regional atrophy within the hippocampus in aging individuals with and without dementia or mild cognitive impairment, with the CA1 subfield showing particular sensitivity. However, no studies to date have considered the potential effects of HT cross-sectionally nor longitudinally with respect to hippocampal subfields.
Methods: The present study assessed total and subfield hippocampal volumes in 54 postmenopausal women at-risk for Alzheimer's disease (AD), all users of HT (either conjugated equine estrogen (CEE) or estradiol) before or within 1-year of menopause. *A priori* risk factors for AD were first-degree family history of AD, known carriership of apolipoprotein epsilon-4 (APOE4), or personal history of major depressive disorder. Subjects underwent brain imaging and cognitive testing at baseline and after 2 years of randomized continuation or discontinuation of existing HT. No other changes were made to any subjects' HT regimen. Total hippocampal volumes and subfield volumes for the CA1, CA2/3, CA4, and subiculum were calculated using *Freesurfer* Version 5 under conditions blind to HT randomization.
Results: All subjects had Mini-Mental Status Scores (MMSE) and IQ scores within the normal range for cognitively intact persons of their same age and level of education. Clinical and demographic characteristics did not differ by use of CEE or estradiol, or by specific a priori risk factors. Baseline total hippocampal and hippocampal subfield volumes did not differ between women HT randomization groups nor by type of estrogen. Increasing age was significantly associated with lower baseline volumes of the right total hippocampus, right CA1, right CA4, right CA2/3, and left subiculum subfields. MMSE scores were not observed to change significantly over the two-year observation period, nor did MMSE score changes differ between HT randomization groups. In repeated-measures general linear modeling, total hippocampal volume was not observed to change significantly over the two-year observation period, nor were there any differences in change by HT randomization or type of estrogen. However, analysis of changes in hippocampal subfields showed a significant interaction was observed for type of estrogen and the right CA1 subfield, as well as a trend interaction with HT randomization, such that the right CA1 subfield was seen to decline in both women who continued and discontinued CEE, increase in women who continued estradiol, and remain relatively unchanged in women who discontinued estradiol. No interactions or main effects of HT randomization or type of estradiol were observed in the remaining hippocampal subfields. Further analysis showed a significant interaction between baseline MMSE and the right total hippocampus, right CA1, and right subiculum. Increased age was also observed to be significantly associated with greater decline in the right total hippocampus, right CA1, right CA2/3, right CA4, and left subiculum subfields. No interactions or main effects were noted for duration of HT use, concurrent use of progestin, or for any of the a priori risk factors.
Conclusions: These findings extend collective understanding of the effects of HT initiated early in menopause, and support previous beneficial findings for estradiol-based HT on the aging female brain. Similar to previous studies on hippocampal subfields in aging populations, the CA1 subfield emerged as most predictive of deleterious decline. These data are the first demonstrating the sensitivity of the CA1 subfield to different types of estrogen-based HT. Further, the current findings of lower MMSE scores at baseline being predictive of greater total and regional hippocampal decline are consistent with numerous previous studies. Previous studies, such as the Womens' Health Initiative Memory Study (WHIMS), have found smaller hippocampal volumes among users of CEE compared to placebo. However, no studies to data have differentially evaluated hippocampal volume change by type of estrogen HT. There is consensus in the field that differences in findings on the effects of HT on hippocampal volume may largely be driven by variation in study samples and cross-sectional studies, with cumulative understanding remaining unequivocal without well-controlled randomized trials with longitudinal neuroimaging. The current results offer a significant advancement toward the goal of improved understanding of the effects of HT on hippocampal volume in postmenopausal women. Additional longitudinal studies with multiple time points may further delineate differential brain effects by estrogen preparation type, and the predictive value of hippocampal biomarkers for AD risk among older women.
Keywords: hippocampal volume, hormone therapy, estrogen, menopause, CA1 subfield
Disclosures: H. Kenna, Nothing to Disclose; K. Sheau, Nothing to Disclose; T. Wroolie, Nothing to Disclose; R. Kelley, Nothing to Disclose; K. Williams, Nothing to Disclose; A. Reiss, Nothing to Disclose; N. Rasgon, Nothing to Disclose.

M46. Effects of Serotonin Depletion on Punishment Processing in the Orbito Frontal and Anterior Cingulate Cortices in Healthy Women

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Background: Diminished synthesis of the neurotransmitter serotonin (5-HT) has been linked todisturbed impulse control in aversive contexts such as decreased punishment inducedinhibition. The present study investigated the underlying neural correlates of punishmentinduced inhibition in young healthy adult females.
Methods: Eighteen healthy women (aged 20 to 31 years) participated in a double-blind,within-subject repeated measures study, with two separate days of assessment. On one dayacute tryptophan depletion (ATD) was used to lower brain 5-HT synthesis. On a further dayparticipants received a tryptophan-balanced amino acid load (BAL) serving as a controlcondition. Three hours after the intake of ATD/BAL, neural activity during punishment-inducedinhibition in a modified Go/No-Go task implementing reward and punishmentprocesses was assessed using functional magnetic resonance imaging (fMRI).
Results: Neural activation underlying No-Go trials in punished conditions after BAL versusATD administration and achieved depletion magnitude correlated positively in the ventral andsubgenual anterior cingulate cortex (ACC). This activation further correlated positively withtrait-impulsivity in the orbitofrontal cortex (OFC) and dorsal ACC.
Conclusions: The present findings indicate lower neural sensitivity to punishment after shorttermdepletion of 5-HT in brain areas related to emotion regulation (such as the subgenualACC) with rising depletion magnitude, and also in brain areas related to executive control(here the OFC and dorsal ACC) with rising trait impulsivity. These preliminary data suggest aserotonergic modulation of relevant brain regions that are engaged in top-down controlledneurocircuitries related to impulsive behavior and punishment processing.
Keywords: Impulsivity, serotonin, tryptophan depletion, Go/No-Go
Disclosures: K. Helmbold, Nothing to Disclose; M. Zvyagintsev, Nothing to Disclose; B. Dahmen, Nothing to Disclose; S. Bubenzer, Nothing to Disclose; T. Gaber, Nothing to Disclose; M. Crockett, Nothing to Disclose; M. Klasen, Nothing to Disclose; C. Sanchez, Nothing to Disclose; A. Eisert, Nothing to Disclose; K. Konrad, Nothing to Disclose; U. Habel, Nothing to Disclose; B. Herpertz-Dahlmann, **Part 1:** Dr. Herpertz-Dahlmann has received industry research funding from Medice and Vifor.; F. Zepf, **Part 4:** Recipient of an unrestricted award donated by the American Psychiatric Association, (APA), the American Psychiatric Institute for Research and Education (APIRE) and AstraZeneca (Young Minds in Psychiatry Award). Recipient of research support from the German Federal Ministry for Economics and Technology, the German Society for Social Pediatrics and, Adolescent Medicine, the Paul and Ursula Klein Foundation, the Dr. August Scheidel Foundation, the IZKF fund, of the University Hospital of RWTH Aachen University, and a travel stipend donated by the GlaxoSmithKline, Foundation. Recipient of an unrestricted educational grant, travel support and speaker honoraria from, Shire Pharmaceuticals, Germany. Recipient of editorial fees from Co-Action Publishing, Sweden. In addition, recipient of support from the Raine Foundation for Medical Research (Raine Visiting Professorship).

M47. Serotonin and Affect Regulation in Humans: A Combined 5-HT1A [11C]CUMI-101 PET and FMRI Study

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Background: Brain serotonin (5-HT) is considered as a key neuromodulator in the processing of aversive events (Dayan and Huys, 2008). Converging evidence suggests that presynaptic dorsal raphe nucleus (DRN) 5-HT_{1A} regulates the 5-HT firing and tone and alterations in the DRN 5-HT1A causes phenotypes characterized by anxiety (Richardson-Jones *et al*, 2011). However, the precise neural mechanisms by which 5-HT1A regulates aversive emotional processing in humans are unclear. The first aim of the present study was to determine if the presynaptic DRN 5-HT_{1A} receptor availability predicts amygdala reactivity during aversive emotional processing. The second aim was to investigate if DRN 5-HT_{1A} is related to the functional connectivity between amygdala and other brain regions involved in the emotion processing.
Methods: We studied 15 healthy participants who underwent a single functional magnetic resonance imaging (fMRI) and a faces-emotion processing task (block design), an incidental task that featured happy, sad and neutral faces (O'Nions *et al*, 2011) known to activate the amygdala. On a separate day, Regional estimates of binding potential (BP_{ND}) were obtained by calculating total volumes of distribution (V_T) for presynaptic dorsal raphe nucleus (DRN) and postsynaptic brain regions. Connectivity was assessed using psychophysiological interaction (PPIs) between the amygdala and emotion processing network (frontal cortex, anterior cingulate, precuneus, fusiform gyrus and parietal cortex) with the amygdala as the seed region. The relationship between PPI connectivity and 5-HT_{1A} DRN availability was investigated by entering the DRN BP values as a covariate in the one-sample t-test analysis of the PPI data.
Results: Blood-oxygen-level-dependent (BOLD) response to fearful *vs* neutral faces in the left amygdala inversely correlated with 5-HT_{1A} DRN availability (Pearson $r = -0.87$, $p < 0.001$) which survived Bonferroni correction and remained significant after excluding one participant with low DRN BP_{ND} ($r = -0.53$, $P = 0.037$). There was no significant relationship between amygdala responses to happy faces and DRN BP_{ND}, $r = -0.34$, $P = 0.21$ and these correlations differed significantly (Steiger's $Z = 2.88$, $P = 0.009$). Connectivity analysis showed that when DRN BP values were entered as a covariate, PPI connectivity directly correlated with DRN 5-HT_{1A} availability in right middle frontal gyrus, anterior cingulate, left-right precuneus, and left inferior parietal lobule, $p < 0.05$, family-wise error (FWE) corrected. PPI parameter estimate and DRN BP correlations were highly significant for all five regions ($p < 0.001$).
Conclusions: The relationship between amygdala responsivity during emotion processing task and baseline dorsal raphe [^{11}C]CUMI-101 binding suggests presynaptic 5-HT_{1A} autoreceptors exerts possibly a tonic serotonergic control

and plays important role in the regulation of affect by modulating emotion processing network. Presynaptic DRN 5-HT_{1A} could be a potential treatment target for affective disorders.
Keywords: serotonin, emotion, 5-ht1a, amygdala, dorsal raphe, nucleus.
Disclosures: S. Selvaraj, Nothing to Disclose; E. Mouchlianitis, Nothing to Disclose; P. Faulkner, Nothing to Disclose; F. Turkheimer, Nothing to Disclose; P. Cowen, **Part 1:** Professor Philip Cowen has been a member of a Lundbeck advisory board for the last two years.; J. Roiser, **Part 1:** Dr Jonathan Roiser has attended Lundbeck media advisory board.; O. Howes, Nothing to Disclose.

M48. Dysregulated Neural Response to Social Evaluation in Bullied Adolescents: A Potential Mechanism that Promotes Risk for Social Anxiety Disorder

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Background: Peer victimization is a risk factor for social anxiety disorder (SAD) that engenders fear of negative evaluation, the primary symptom of SAD. While available treatments for SAD can reduce symptoms, they rarely result in full remission. Interventions that target neural circuits dysregulated in adolescent SAD may enhance treatment efficacy. An important first step toward developing such interventions is to isolate dysregulated neural circuits shared by early adolescents with SAD, and at risk for SAD due to peer victimization. Treating early adolescents may alleviate acute symptoms before they become chronic, thereby facilitating normative development, and preventing the high cost of adult SAD. Progress toward this goal has been hindered by limitations in neuroimaging paradigms, which bear little resemblance to contexts that precipitate the primary symptoms of adolescent SAD, or to contexts in which peer victimization occurs. An fMRI paradigm that evokes fear of negative evaluation while modeling an ecologically valid context for bullying may address these limitations, and thereby facilitate the development of novel interventions. To this end, we developed the Virtual School paradigm, which explicitly models unpredictable social evaluation in an ecologically valid classroom setting. Here we present data from the first fMRI study to utilize the Virtual School paradigm. In this study, we assess brain function as healthy adolescents with high or low exposure to victimization anticipate social evaluation from predictable and unpredictable peers. We hypothesize that adolescents with high, relative to low, exposure to peer victimization will differentially engage fronto-striatal-amygdala circuits, implicated in self-reflection, reward, and threat processing, when anticipating unpredictable social feedback from peers.
Methods: Healthy adolescents ($N = 22$; $M = 10.73$ years; $SD = 0.46$) with high and low exposure to peer victimization are told that they are the 'New Kid' at our Virtual School. They generate a cartoon avatar and personal profile they believe will be shown to a purported group of 'Other Students.' Participants learn the Other Students have a reputation for being 'Nice,' 'Unpredictable,' or 'Mean.' Reputation comprehension is assessed prior to completing the Virtual School paradigm in the fMRI scanner.During the task, participants enter classrooms populated by Other Students. For each trial, participants are cued to anticipate social evaluation when 'Typing...' appears above one of the Other Students. Because Other Students have an established reputation, participants anticipate different types of social evaluation from each peer. Unpredictable peers then provide 50% positive and negative feedback, while Nice and Mean peers provide 100% positive or 100% negative feedback (respectively). Participants then make a positive, negative, sarcastic, or avoidant response to peer social evaluation.
Results: Replicating prior behavioral findings (Jarcho *et al*, 2013), adolescents learned Other Student reputations, made responses during the task that varied by peer reputation and feedback, and believed they were interacting with real peers (100% deception). As hypothesized, brain activity during anticipated social evaluation varied based on participant exposure to peer victimization and Other Student reputation ($p < 0.005$; cluster extent > 70 voxels). Specifically, while anticipating unpredictable, relative to predictable positive or negative social evaluation, victimized adolescents exhibited heightened activity in fronto-striatal-amygdala circuits compared with non-victimized adolescents.
Conclusions: Exposure to peer victimization is associated with differential engagement of a brain network implicated in self-reflection, reward, and threat processing. This engagement varies depending on the type of social evaluation (i.e., uncertain vs. certain) victimized adolescents anticipate. These data suggest one mechanism by which exposure to bullying may lead to SAD is through disruptions in neural circuits engaged by unpredictable social evaluation. Longitudinal studies are needed to more fully test this hypothesis.
Keywords: fMRI, peer victimization, adolescence, social evaluation
Disclosures: J. Johanna, Nothing to Disclose; M. Davis, Nothing to Disclose; E. Leibenluft, Nothing to Disclose; N. Fox, Nothing to Disclose; T. Shechner, Nothing to Disclose; D. Pine, Nothing to Disclose; E. Nelson, Nothing to Disclose.

M49. Prenatal Exposure to Maternal Infection Alters Neonatal Brain Structure

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Background: Prenatal exposure to maternal infection is a risk factor for neuropsychiatric disorder. Studies in animal models suggest that prenatal exposure to infection causes significant alterations in structural brain development, though studies in humans are lacking.
Methods: Prospective, longitudinal follow-up study of a cohort of 445 infants, both singleton and twins, born to women assessed for infection during pregnancy by prospective interviews and medical records review. At 2 weeks after birth infants underwent 3 T MRI scans. Global and cortical tissue volumes were determined.
Results: Neonates exposed to maternal infection had a significant reduction in cortical gray matter (1.9%; $p = 0.04$) and non-significant reductions in intracranial volume (ICV;

1.5%; p = 0.11) and total gray matter (1.65%; p = 0.07) compared to infants with no exposure. Infants with first exposure to infection in the third trimester had significant reductions in ICV (3.5%; p = 0.02), total gray matter (4.1%; p = 0.004), unmyelinated white matter (3.6%, p = 0.03), as well as cortical gray (4.9%; p = 0.0008) and cortical white matter volumes (3.5%; p = 0.03).

Conclusions: Prenatal exposure in maternal infection results in cortical gray matter volume reductions, especially for first exposure to infection in the 3rd trimester. This study indicates that prenatal exposure to infection can significantly alter prenatal brain development in humans, providing a plausible mechanistic basis for the relationship between prenatal exposure to infection and increased risk for neuropsychiatric disorders.

Keywords: magnetic resonance imaging, brain development, infection infants

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M50. Memory Retrieval of Addiction-Related Images Induce Greater Insular Activation as Revealed by an fMRI Based Delayed Matching to Sample Task

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Background: Environmental stimuli associated with drugs of abuse precipitate craving and relapse. How stimuli that induce craving are cognitively processed may provide insight into the persistence of reactivity to drug-related stimuli. We focused on working memory differences between drug-related and neutral stimuli, as working memory is the process by which information is temporarily stored and manipulated (Baddeley, 2003). To evaluate working memory differences between stimuli type, we conducted a delay-match-to-sample (DMS) task concurrently with functional magnetic resonance imaging (fMRI) in nicotine dependent participants. The DMS task evaluates brain activation during the encoding, maintenance, and retrieval phases of working memory.

Methods: Eighteen nicotine-dependent smokers (8 men/10 women) between the ages of 18–33 completed all study measures at the McLean Imaging Center of McLean Hospital. Participants reported smoking $\geqslant$ 10 cigarettes/day over the past 6 months and were moderately to heavily nicotine dependent as measured by the Fagerstrom test for nicotine dependence (Fagerström, 1978). Scans were acquired on a Siemens Trio 3 Tesla scanner. Smoking and neutral images were used in the DMS task where participants were shown a sample image, followed by a delay and then a test image. Using a button box, participants were asked to determine whether the test image matched or did not match the sample image. Contrasts were created between the smoking and neutral image conditions at the sample, delay, test match and test non-match periods. Statistical significance was cluster corrected to $p < 0.05$. All images were subjectively evaluated based on craving, affect, and arousal.

Results: Participants reported significantly greater levels of cigarette craving when viewing smoking vs. neutral images ($t_{(17)} = 7.1$, $p < 0.0001$), while no difference between image type was found for affect and arousal. During the sample (memory encoding) period, significant activation was evident for the smoking > neutral contrast primarily in cortical midline structures. Memory maintenance was assessed during the delay period, which revealed that there was significant activation for the neutral > smoking contrast in bilateral ventrolateral (VLPFC) and right dorsolateral prefrontal cortex (DLPFC) and right putamen. During the test period significant activation was found during the smoking > neutral match contrast in the left insula cortex extending into the inferior frontal gyrus.

Conclusions: During encoding of smoking vs. neutral images, enhanced brain activation was noted in cortical midline brain regions, which show strong overlap with patterns of brain activity reported during self-referential processing. For the neutral vs. smoking image contrast during the maintenance phase, more activity was found in the DLPFC and VLPFC, which are brain regions involved in actively maintaining memory across a delay. Finally, during the retrieval of previously viewed smoking vs. neutral images, the left insula cortex showed greater activation. The insula has been implicated in maintaining nicotine dependence (Naqvi *et al*, 2007), as well as associations between visceral drug effects and drug-related stimuli (Conteras *et al*, 2012; Forget and Le Foll, 2010; Janes *et al*, 2010) making it likely that the insula plays a role in memory for stimuli that induce visceral states such as craving. While not traditionally thought of as a memory center of the brain, the insula may impact memory through its rich interconnections with temporal lobe structures (Augustine *et al*, 1996) and this region has been implicated in various forms of memory (Ross and Slotnick 2008; Levens and Phelps., 2010; Bermudez-Rattoni and McGaugh, 1991). The present results offer strong evidence that different brain areas are engaged during working memory for addiction-related images that trigger craving. When smoking images are presented to smokers, they are encoded as self-relevant, require less active maintenance across a delay, and may rely on insula mediated internal states for their successful recognition. We suggest these differences result from the strong interoceptive states induced by smoking images in nicotine-dependent individuals.

Keywords: craving, insula, drug addiction, memory, nicotine dependence, fMRI

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M51. Nicotinic Acetylcholine Receptor Density as a Predictor of Quitting Smoking with Treatment

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Background: Up-regulation of nicotinic acetylcholine receptors (nAChRs), including the common α4β2* nAChR subtype, is one of the most well-established effects of smoking on the human brain. While subjective aspects of tobacco dependence have been extensively examined as predictors of quitting smoking with treatment, we are not aware of studies determining the relationship between pre-treatment up-regulation of nAChRs and smoking cessation with a standard course of treatment.
Methods: 81 tobacco-dependent smokers underwent positron emission tomography (PET) scanning with the radiotracer 2-FA (for labeling α4β2* nAChRs) followed by double-blind treatment with either active nicotine (n = 41) or placebo (n = 40) patch for 10 weeks (random assignment). In addition to PET scanning, participants also completed the Fagerstrom Test for Nicotine Dependence, Urge to Smoke (craving) scale, and a self-efficacy rating scale prior to treatment, in order to examine well-known predictors of treatment response. Quit status was defined as a participant report of $>$ 1 week of smoking abstinence and an exhaled carbon monoxide level of $<$ 3 parts per million at the final study treatment visit.
For the primary study analysis, an overall multivariate analysis of covariance (MANCOVA) was performed using total binding volume of distribution (V_T/f_P) values for eight regions of interest (ROIs) as the measures of interest, treatment subgroup (placebo or nicotine patch) and quit status as factors, and age as a nuisance covariate (since prior research indicates that nAChR densities decline with age). Follow-up ANCOVAS were performed for the ROIs separately with the same variables as for the overall MANCOVA. For descriptive purposes, mean $\alpha_4\beta_2^*$ nAChR densities for quitters and non-quitters were compared to available values from non-smoking controls in a previous study, and the percentage up-regulation of $\alpha_4\beta_2^*$ nAChR densities for both groups was calculated.
In order to determine which pre-treatment factors best predicted quit status, binary logistic regression was also used, as in prior studies, with quit status as the outcome variable and pre-treatment PET V_T/f_P data (mean of all ROIs), severity of nicotine dependence (FTND score), subjective craving (mean UTS score on a scale of 0 to 6), and self-efficacy ratings (on a scale of 0 to 100) as the predictor variables. Statistical tests were performed using PASW/SPSS Statistics version 21.0 (SPSS, Inc., Chicago, IL).
Results: 20 of the 81 participants met full criteria for having quit smoking at the end of treatment, with a higher percentage of participants treated with active patch having quit smoking than those treated with placebo patch (34.1 versus 15.0%, Chi-Square test, $p < 0.05$).
The overall MANCOVA examining the relationship between pre-treatment $\alpha_4\beta_2^*$ nAChR density and quit status revealed a significant main effect of pre-treatment V_T/f_P values on quit status ($F\ [8,69] = 3.9$, $P = 0.001$), resulting from quitters having lower pre-treatment V_T/f_P values than non-quitters. All ROIs had significant associations with quit status (Fs [1,80] = 11.4 to 18.8, Ps = $<$0.0005 to 0.001), indicating that the relationship between pre-treatment nAChR density and quitting with treatment was not region specific. The interaction between treatment type and quit status was not significant ($F\ [8,69] = 0.3$, n.s.), indicating that the relationship between pre-treatment nAChR density and quit status was not dependent on treatment type. For the brainstem and prefrontal cortex, quitters had 14 and 21% up-regulation of nAChRs (respectively) compared to previously scanned non-smoking controls, while non-quitters had 42 and 52% up-regulation in these regions.
For the logistic regression analysis, the overall test of the ability to use pre-treatment variables to predict quitting was highly significant (Chi-square = 30.3, df = 4, $p < 0.0005$). Low mean pre-treatment pre-treatment PET V_T/f_P values (9.6 versus 14.9; $p < 0.0005$), low mean craving (UTS) scores (2.2. versus 3.4; $p = 0.003$), and high self-efficacy scores (60 versus 46; $p = 0.02$) were all associated with quitting, while low nicotine dependence (FTND) score had the expected directional relationship, but did not reach statistical significance (4.0 versus 4.6; $P = 0.25$).
Conclusions: Cigarette smokers with less severe up-regulation of brain $\alpha_4\beta_2^*$ nAChR density have an improved chance of quitting smoking with treatment than smokers with more severe up-regulation of these receptors. This finding was present in smokers treated with nicotine and placebo patch, and is consistent with our prior preliminary evaluation of smaller groups of smokers treated with cognitive-behavioral therapy, bupropion HCl, or pill placebo. Furthermore, this study supports the use of other measures (severity of nicotine dependence, level of craving, and self-efficacy) in the prediction of treatment response, but the association between the biological marker measured here (up-regulation of $\alpha_4\beta_2^*$ nAChRs) and quit status was numerically more highly significant than the associations between subjectively-rated symptoms and quit status.
Keywords: Tobacco Dependence; Nicotinic Acetylcholine Receptor; Nicotine Patch; Nicotine Replacement Therapy; Positron Emission Tomography
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M52. Striatal Activation Induced by mGluR2 Positive Allosteric Modulation Correlates with Negative Symptom Reduction in Schizophrenia

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Background: Cognitive deficits and negative symptoms contribute strongly to disability in schizophrenia, and are resistant to existing medications, creating a critical need for novel therapeutic targets and agents. Inspired by the glutamate hypothesis, recent drug development efforts have focused on ameliorating putative deficits in NMDA signaling. In animal models, mGluR2/3 agonists and mGluR2 positive allosteric modulators (PAMs) have reversed the physiologic and behavioral effects of NMDA receptor antagonists. However the clinical utility of such agents remains uncertain, and their impact on neural circuit function in humans remains unknown. Progress in this area will benefit from studying novel agents targeting cognition and negative symptoms using integrative paradigms that incorporate clinical, neurocognitive performance and neurophysiological measures in order to evaluate early signals of efficacy. We therefore performed this fMRI study as part of a Phase 1 pilot study (NCT00986531) evaluating the mgluR2 PAM AZD8529 as an adjunctive treatment for cognitive deficits and negative symptoms. We hypothesized the drug would improve cognition and symptoms, and that clinical improvements would correlate with changes in fMRI activation.
Methods: Subjects with complete fMRI data were 26 patients (10 female) with DSMIV schizophrenia, stably treated with antipsychotics. 3 T MRI scanning was performed following three days treatment with AZD8529 (80 mg once-daily) or placebo. The study design was double blind, placebo-controlled, counterbalanced within-subject crossover, with a 14-day washout between drug and placebo phases. During fMRI scanning, subjects performed a fractal n-back task (0, 1, 2, and 3-back block design), as well as a continuous performance task and an emotion identification task. We focus here on the n-back task; the other two tasks did not show signficant drug effects. fMRI analysis focused on task-activated regions of interest including anterior cingulate (ACC) and dorsolateral prefrontal cortex (DLPFC). Exploratory whole-brain voxelwise analyses were also conducted to test for drug effects outside of the a priori ROIs.
Results: No significant effects of drug were found on average clinical symptoms or on behavioral performance during in-scanner or out-of-scanner tasks. BOLD activation in DLPFC and ACC showed expected increases with working memory load. Relative to placebo, drug increased activation in ACC ($p = 0.031$). Although activation trended higher on drug in left and right DLPFC there was no significant main effect of drug in these regions. An exploratory whole brain analysis demonstrated the most robust drug effects in basal ganglia; we therefore also conducted region of interest analyses in in right and left caudate, putamen, and pallidum. The main effect of drug was significant in all these regions due to increased activation by drug compared to placebo (L Caudate, $p < 0.001$; R Caudate $p < 0.001$; L Putamen $p = 0.0014$; R Putamen $p < 0.001$; L Pallidum $p = 0.017$; R Pallidum $p < 0.001$). No regions showed significant interaction effects of drug with working memory load level. Subjects who showed greater caudate activation by the drug also showed greater reductions in PANSS negative symptom scores (correlation of drug-placebo difference scores, $r = -0.47$, $p = 0.02$). A similar trend was seen in the putamen ($r = -0.37$, $p = 0.06$), but not in other drug-activated regions, suggesting the symptom-activation correlation was specific to striatum.
Conclusions: The mGluR2 PAM was generally well-tolerated. In this pilot study the drug did not significantly improve cognitive performance, nor did it reduce clinical symptoms on average. However, the drug did increase fMRI activity in the anterior cingulate and basal ganglia during a working memory task, and the extent of drug-induced striatal activation correlated with reductions in negative symptom severity. These results encourage further investigation of this mgluR2 PAM and related agents, including studies focused on the potential role of striatal mechanisms impacting emotion and motivation. Our results also support the use of fMRI for sensitive detection of drug effects. Imaging biomarkers may reveal therapeutic mechanisms, and help tailor drug development and treatment towards specific patient populations and symptom domains.
Keywords: schizophrenia, negative symptoms, metabotropic glutamate receptor, fMRI, striatum
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M53. Olfactory Functional Magnetic Resonance Imaging (fMRI) in Combat Veterans: Brain Reactivity to Trauma-related Odor Cues

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Background: Case reports suggest that trauma-related odors can trigger PTSD symptoms. However, little empirical data exists on this topic.
Methods: Twelve Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) combat veterans with posttraumatic stress disorder (PTSD) and 11 healthy OEF/OIF combat veterans (HV) participated in this study, which consisted of 2 phases: 1) documentation of combat history, clinical assessment, and baseline odor ratings, and 2) olfactory fMRI. During baseline odor testing, veterans were systematically presented with a combat-related odor (burned rubber, BR), and 2 non combat-related odors [lavender (LAV) and propylene glycol (PG, an odorless control)]. Visual analog scales (100 mm) were used to measure the degree to which odors evoked positive and negative emotions, as well as memories of their traumatic combat experiences. All participants then underwent olfactory fMRI during which BR, LAV, and PG were systematically delivered. Contrast maps for BR and LAV were derived against PG, as well as each other. All fMRI analyses were conducted in FSL.
Results: *Demographics and odor trauma history*: The PTSD and HV groups were nearly all male (PTSD: 9 M/1 F, HV: 13 M) and of similar age [PTSD: $M = 31.1$ ($SD = 9.6$), HV: $M = 30.5$ ($SD = 8.3$)]. The groups differed significantly on the total score of the Clinician Administered PTSD Scale (CAPS) [PTSD: $M = 63.3$ ($SD = 21.6$), HV: $M = 13.2$ ($SD = 7.4$), $p < 0.05$], but did not differ with respect to the level of combat exposure [PTSD: $M = 18.1$ ($SD = 10.8$), HV: $M = 21.4$ ($SD = 9.0$), $p > 0.1$], or the number of additional traumatic events experienced during their lifetime [PTSD: $M = 3.5$ ($SD = 1.5$), HV: $M = 2.8$ ($SD = 1.2$), $p > 0.1$]. Nearly all participants ($>90\%$) associated odors with their combat-related experiences. The most commonly reported odors were burned rubber/tires and burning waste/burn pit. There was no difference in associating BR with combat-related events between those with versus without PTSD. *Baseline odor ratings:* Repeated measures ANOVA on the subjective odor ratings revealed significant main effects of odor condition. As expected, BR was rated significantly less pleasant than either LAV or PG ($p < 0.05$). And, consistent with their odor trauma history, BR, administered under blind conditions, evoked significantly greater feelings of being 'irritated' ($p < 0.05$), and was significantly more effective at evoking traumatic combat memories than either LAV or PG ($p < 0.05$). Further analysis revealed a significant 'BR-evoked memories' by 'diagnosis' interaction ($p < 0.05$), which was a consequence of mainly the combat veterans with PTSD reporting BR-evoked memories of trauma. *Olfactory fMRI:* As a group (collapsed across diagnosis), combat veterans demonstrated significant activation in response to BR (BR minus LAV contrast) in the anterior cingulate and paracingulate gyrus, as well as left insula that extended into left orbitofrontal cortex (clusters determined by $Z > 2.3$, corrected cluster threshold $p = 0.05$). Conversely, no significant activation was demonstrated in response to LAV (LAV minus BR contrast, clusters determined by $Z > 2.3$, corrected cluster threshold $p = 0.05$).
Conclusions: A clear dissociation between the effects of lavender and burned rubber odors on self-reported measures related to combat trauma and fMRI BOLD response in OEF/OIF combat veterans was demonstrated in this study. Despite the fact that burned rubber was rated more negatively than lavender for all participants, only those veterans diagnosed with PTSD reported BR-evoked traumatic memories. Group differences (PTSD versus HV) in BR-elicited regional BOLD activation, as well as the relationship between BR-elicited regional BOLD activation and the baseline odor ratings, are currently being explored.
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Keywords: posttraumatic stress disorder odor cues combat veterans fMRI cue-reactivity
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M54. Methylphenidate and Brain Activity in a Reward/Conflict Paradigm

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Background: Existing evidence suggests that motivation-reward and attention-activation networks function in concert and that activation in one system reciprocally influences the other. Moreover, psychostimulants like methylphenidate, are thought to improve information processing in these networks by enhancing the effects of relevant signals and suppressing less relevant ones. The nature of such reciprocal influences, however, remains poorly understood. To explore this question we developed a novel hybrid task, called Anticipation, Conflict, Reward (ACR) task, that has three distinct components—reward anticipation, conflict resolution, and reward outcomes—that aim to index activation and interactions among regions of the brain motivation - reward and attention-activation systems. Further, we tested the effect of methylphenidate on performance and associated brain activity during the ACR task.
Methods: Sixteen healthy adult volunteers, ages 21–45 (Mean −30.6, SD + 7.4), were scanned twice using functional magnetic resonance imaging (fMRI) as they performed the ACR task under placebo and methylphenidate conditions. A three-way repeated measures analysis of variance, with cue (reward vs. no reward), target (congruent 'easy' vs. incongruent 'difficult') and medication condition (methylphenidate vs. placebo) as the factors, was used to analyze behavior on the task. Blood oxygen level dependent (BOLD) signals reflecting task-related neural activity were evaluated using the appropriate linear contrasts (i.e. reward minus non-reward cue; congruent minus incongruent target, expected reward minus expected non-reward, surprising minus expected non-reward).
Results: Behaviorally participants exhibited significantly greater accuracy in the methylphenidate than the placebo condition. Neuroimaging results show that the insula cortex was robustly engaged during the cue-by-target interactions and the surprising non-reward outcomes. In addition, the methylphenidate condition was associated with lower task-related activity in components of attention-activation systems irrespective of the reward cue. Similarly methylphenidate was associated with lower task-related activity in

components of the reward-motivation system, particularly the insula, during reward trials irrespective of target difficulty.
Conclusions: These results suggest that methylphenidate enhances task performance by improving efficiency of information processing in both reward-motivation and in attention-activation systems. Moreover, these effects appear to be influenced by activation in the insula cortex. We further suggest that methylphenidate may contribute to change of strategy in order to optimize outcomes. This is supported by observations that in the placebo condition participants commit the most effort to minimize loss; conversely with methylphenidate they commit most effort to obtain both 'easy' and 'difficult' rewards, which resulted in improved outcomes. In summary this work offers new insights on the effects of psychostimulants on motivation and executive control relevant to conditions like ADHD, depression and substance use.
Keywords: motivation, cognitive control, fMRI, methylphenidate, insula
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M55. Being Liked Increases Social Motivation, but Not in Depressed Individuals: A μ-Opioid Positron Emission Tomography (PET) Study of the Ventral Striatum

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Background: Animal work shows that μ-opioid receptor (MOR) signaling in the ventral striatum plays a role in social reward. In the present study, we hypothesized that patients with major depressive disorder (MDD) compared to healthy controls would have an altered behavioral and MOR response in the ventral striatum during social acceptance (i.e., being liked by others).
Methods: Participants were 17 medication-free patients with current MDD (13 females, 4 males; mean age ± SD, 30 ± 10 years) and 18 healthy controls (13 females, 5 males; 32 ± 12 years). MDD patients were diagnosed by structured clinical interview, scored > 14 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 were most likely to form a close relationship. A few days later they were given feedback that they were liked by 12 of their highest-rated profiles (acceptance block) during positron emission tomography (PET) with intravenous administration of the selective MOR radiotracer [^{11}C]carfentanil. Within the same individuals acceptance blocks were compared with baseline blocks, which contained a similar visual presentation but with no feedback. Block order was randomized and counterbalanced across subjects. MOR activation levels extracted from the ventral striatum were compared between groups and correlated with behavior. Behavioral measures included the Desire for Social Interaction (DSI), which included items such as 'I would enjoy social interaction right now' and 'right now, I have a strong desire to meet new people.' Subjects also reported how 'happy' and 'accepted' they felt during and immediately after the acceptance and baseline blocks.
Results: Prior to scanning (at 'rest'), MDD patients had a reduced DSI compared to healthy controls ($t_{31} = 7.62$, $P < 0.0000001$). During the acceptance block, MDDs reported feeling significantly more 'happy' and 'accepted' over baseline compared to healthy controls (due to lower baseline levels of happiness in MDDs), however at the end of the blocks these increases were not significantly different than in controls. Immediately after the acceptance block, healthy controls but not MDDs reported a greater DSI over baseline (controls, $t_{15} = 2.91$, $P = 0.01$). MOR activation in the left or right ventral striatum was not significantly different between MDD and controls. MOR activation in the left ventral striatum was positively correlated with DSI levels in healthy controls (left NAcc: $r = 0.60$, $P = 0.01$; right NAcc: $r = -0.04$, $P = 0.89$), but not in MDD (left NAcc: $r = 0.50$, $P = 0.86$; right NAcc: $r = 0.04$, $P = 0.87$).
Conclusions: Patients with MDD have significantly reduced social motivation at 'rest.' Although being liked by others may temporarily increase positive emotions in MDD, these emotions are fleeting and do not appear to increase social motivation. Subtle aspects of dysfunction in MOR signaling between MDD and healthy controls in the left ventral striatum may be driving these differences.
Keywords: social acceptance opioid PET depression
Disclosures: D. Hsu, Nothing to Disclose; B. Sanford, Nothing to Disclose; K. Meyers, Nothing to Disclose; K. Hazlett, Nothing to Disclose; T. Love, Nothing to Disclose; B. Mickey, Nothing to Disclose; S. Langenecker, Nothing to Disclose; J. Zubieta.

M56. Prediction Error Reactivity and Its Relation to Reward Expectancy are Altered in Major Depressive Disorder: Preliminary Findings from the EMBARC Study

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Background: Neuroimaging research has consistently implicated the ventral striatum and medial frontal regions including anterior cingulate cortex (ACC) in mediating responses to reward expectancy and outcomes. Recent findings demonstrate altered reward-related activation in these regions in patients with major depressive disorder (MDD) representing potential neural markers that may aid diagnosis and prediction of treatment response. Here, we compared neural reactivity in a group of unmedicated patients with MDD and a group of healthy individuals, recruited for a large multi-site study (EMBARC), using a

well-validated card guessing task (Forbes *et al*, 2009) that allows a detailed examination of reward-related neural responses including reward expectancy and prediction error responses and their association.

Methods: Forty-three patients (30 females, 13 males; Mean age = 38.6, SD = 13.25) with MDD and 31 healthy individuals (19 females, 12 males; Mean age = 38.42, SD = 15.74) were included in the analysis. The two groups were matched for age, sex, marital status and level of education. All patients had a Hamilton Rating Scale for Depression score (HRSD-24) $\geqslant$ 12 (M = 26.51, SD = 6.22). Mean scores on the Snaith-Hamilton Pleasure Scale (SHAPS) and the Spielberger State Anxiety Inventory (STAI-S), administered on the day of the scan session, were (SHAPS: M = 5.67, SD = 3.23; STAI: M = 47.84, SD = 10.27) for the patient group and (SHAPS: M = 1.45, SD = 1.33; STAI: M = 23.84, SD = 4.44) for the healthy group. The reward task included 24 trials presented in pseudorandom order with predetermined outcomes. There were four possible trial types: the expectation of a possible win, followed by a win outcome or no change outcome, and the expectation of a possible loss, followed by a loss outcome or no change outcome. We conducted a region of interest (ROI) analysis focused on the dorsal anterior cingulate (dACC) and the ventral striatum, based on a previous report in patients with mood disorders using the same task (Chase *et al*, 2013), in order to investigate group differences in reward expectancy (RE) and prediction error (PE) related activation. In addition, we conducted correlational analysis to examine the relationship between RE and PE reactivity in the two groups.

Results: Patients with MDD, compared to healthy individuals, exhibited reduced PE reactivity in the dACC ($F(1,70) = 10.04$, $p = 0.002$). There were no group differences in RE related activation (both ps > 0.5). Examination of the relationship between RE and PE reactivity showed a significant negative correlation in the right ventral striatum in healthy individuals ($r = -.39$, $p = 0.03$) but no association in patients ($r = -.04$, $p = 0.8$).

Conclusions: Our findings demonstrate deficient reward-related ACC response in a large sample of unmedicated patients with MDD. This is consistent with previous reports of altered ACC reactivity in MDD and provides strong support for its involvement in the pathophysiology of this disorder. Patients and healthy individuals exhibited similar RE related activation. However, the two groups showed marked differences in the relationship between RE and PE reactivity. Whereas the negative correlation observed in the healthy group is in line with predictions of the temporal difference model, the absence of this association in the patient group is suggestive of less adaptive contingency learning that may contribute to the development of symptoms. The identification of these distinct neural responses in a large clinical sample provide an important step in elucidating potential biosignatures of MDD that may aid prediction of treatment outcome.

Keywords: mood disorder, reward, anticipation, prediction error, ACC, ventral striatum, fMRI

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M57. In vivo Neurochemical Effects of Ketamine in OCD: A Pilot Proton Magnetic Resonance Spectroscopy Time-course Study of Cortical Glutamate-glutamine and GABA

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Background: Obsessive-compulsive disorder (OCD) is a leading cause of illness-related disability. Structural and functional imaging studies suggest that OCD is associated with abnormal functioning of a brain circuit that includes the orbito-frontal cortex (OFC), anterior cingulate cortex (ACC), striatum, and thalamus, known as the cortico-striato-thalamo-cortical (CSTC) circuit. Recent data suggests there are abnormalities in the glutamatergic system and γ-aminobutyric acid (GABA) system. A single intravenous sub-anesthetic dose of ketamine, a non-competitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, has been shown to have rapid and sustained anti-OCD effects without the presence of a serotonin reuptake inhibitor in a small randomized controlled trial, but the mechanism of action of these rapid behavior effects remains unknown. Ketamine has been shown to modulate Glx (a composite measure of glutamate and glutamine) and GABA in healthy controls and individuals with major depression using proton magnetic resonance spectroscopy (MRS). Yet, no study has investigated Glx and GABA changes following ketamine administration in an OCD population. Using MRS, we investigated for the first time Glx and GABA changes following ketamine versus saline administration in individuals with OCD focusing on one node of the CSTC circuit, a medial prefrontal cortex (MPFC) voxel containing the pregenual ACC (pgACC).

Methods: In a randomized, double-blind, placebo-controlled, crossover design, unmedicated adults ($N = 17$) with OCD received two intravenous infusions: one of saline and one of ketamine (0.5 mg/kg) over 40 min while lying supine in a 3.0 T GE MR scanner. These infusions were spaced at least 1 week apart and the order of each pair of infusions was randomized. To be eligible, participants were required to have at least moderate to severe OCD (Yale-Brown Obsessive-Compulsive Scale [YBOCS] score > 16) with absent or mild depression (Hamilton Depression Rating Scale [HDRS-17] < 25). Six 13-min scans were collected at baseline, during, and following the ketamine infusion to establish a time course. An 8-channel phased-array head coil and volume-selective PRESS J-editing difference method was used to measure Glx (a composite of glutamate and glutamine) and GABA levels in the medial prefrontal cortex (MPFC), including pgACC. A mixed-effects linear model was used to analyze the effects of normalized Glx and GABA levels (ratios relative to voxel tissue water [W] in MPFC) as a function of infusion type ($=1$ for ketamine, $=0$ for placebo), infusion order ($=1$ for ketamine first, $=0$ for placebo first), time, and interactions with subject as a random effect and frame as a fixed effect.

Results: All 17 participants completed the study. 1 participant was excluded from analysis as an outlier due to Glx/W levels that were greater than 3 standard deviations from the mean at baseline. In the MPFC, Glx/W did not differ by treatment type (ketamine versus saline) over time ($p > 0.6$), considering frame as a factor (all p's > 0.1). In the MPFC, GABA/W showed trending differences in treatment type over time ($p = 0.065$). Pairwise comparisons of ketamine versus saline revealed a significant difference at scan 5 only ($p = 0.0279$), approximately 60–75 min after the start of infusion. Additionally, a pairwise comparison between baseline ketamine scan and scan 5 after ketamine infusion also revealed a significant difference ($p = 0.0295$).

Conclusions: We found a transient increase in GABA at 60–75 min post-ketamine infusion start in adults with OCD in a MPFC voxel that included the pgACC. This is the first report to show an *in vivo* time-course of the neurochemical effects of ketamine in OCD. A recent study has shown individuals with OCD have lower levels of GABA at baseline in pgACC. Thus, ketamine's ability to increase GABA levels may highlight a novel mechanism of action of ketamine in OCD and provides rationale for future studies of how GABA abnormalities might contribute to CSTC circuitry dysfunction.

Keywords: Ketamine, OCD, Glutamate, GABA, MRS
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M58. Subcortical Biophysical Abnormalities in Patients with Mood Disorders

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Background: Cortical-subcortical circuits have been implicated in the pathophysiology of mood disorders. Structural and biochemical abnormalities have been identified in patients diagnosed with mood disorders using magnetic resonance imaging (MRI) related approaches. In this study, we used magnetization transfer, an innovative MR approach, to study biophysical changes to the macromolecular protein pool in both gray and white matter regions in cortical-subcortical circuits implicated in emotional regulation and behavior.
Methods: Our study samples comprised 28 patients clinically diagnosed with major depressive disorder (MDD) and 31 non-depressed subjects of comparable age (MDD: 57.89 ± 13.27; non-depressed: 59.13 ± 15.71) and gender(MDD: 9 M/19 F; non-depressed: 10 M/21 F) . The MRI was performed on a Philips Achieva 3 T scanner with a Philips SENSE-Head 8 Coil. MT and DTI images were processed as previously described (Kumar *et al*, Molecular Psychiatry 2013). Magnetization Transfer Ratio (MTR), representing the biophysical integrity of macromolecular proteins within key components of cortical-subcortical circuits - the caudate, thalamic, striatal, orbitofrontal, anterior cingulate and dorsolateral regions - was the primary outcome measure. Preclinical studies demonstrate that lower MTRs are associated with damage to axons/myelin in the white matter and to the macromolecular protein pool in the gray matter. Group differences in MTR were assessed using ANCOVA controlling for age and sex. Correlations between the MTRs and age were analyzed using partial Pearson's product-moment correlations.
Results: In our study, the MTR in the head of the right caudate nucleus was significantly lower in the MDD group when compared with the comparison group (Healthy controls: mean $= 0.468 \pm 0.02$; MDD: mean $= 0.454 \pm 0.022$; $F(1,55) = 7.746$; $p = 0.007$; Cohen's $d = 0.687$). MTR values showed an inverse relationship with age in both groups, with more widespread relationships observed in the MDD group (e.g., right putamen [HC: $r = -0.509$, $p = 0.003$; MDD: $r = -0.557$, $p = 0.002$]).
Conclusions: These data indicate that focal biophysical abnormalities to proteins in the caudate nucleus may be central to the pathophysiology of depression and critical to the cortical-subcortical abnormalities that underlie mood disorders. Depression may also accentuate age related changes in the biophysical properties of cortical and subcortical regions. These observations have broad implications for the neuronal circuitry underlying mood disorders across the life span.
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Keywords: depression, magnetization transfer, imaging, mood disorders, caudate nucleus
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M59. Accounting for Dynamic Fluctuations Across Time When Examining Test-Retest Reliability: Analysis of a Reward Paradigm in the EMBARC Study

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Background: The extant neuroimaging literature describing the test-retest reliability of different paradigms is highly inconsistent. In previous work using functional magnetic resonance imaging (fMRI) of a reward paradigm, we have examined the neural response in ventral striatum (VS) to positive prediction errors—events when an outcome is more rewarding than was expected. In addition to observing a robust response in this region in healthy control (HC) participants, we observed a negative correlation between the magnitude of this response and the activation in the VS associated with a prior cue which signaled the likelihood of obtaining reward. This finding is intriguing as because it reflects the 'temporal difference' model of learning and a dominant account of ventral striatum function. The key prediction that these models make is that reward-related activation is represented as a deviation from expectation, and reflects whether an event is better or worse than expected (a 'signed prediction error'). In addition, with training, this prediction error signal moves backwards in time to the earliest reliable predictor of reward. With regard to the test-retest reliability of reward-related activation within the VS, the temporal difference model provides testable estimates of variation in the within and between participant reliability of VS activation, and failure to account for this dynamic process could lead to excessively pessimistic evaluations of the reliability of the task. Put

simply, although variation in activation levels from the first to second scanning session will lead to low estimates of reliability using intraclass correlations (ICCs) or similar measures, such variation may be *predictable* insofar as it accords with theoretical models of functioning in reward systems. Longitudinal investigations of the neural basis of reward processing in depression may represent a useful paradigm for defining effective biomarkers for antidepressant treatment prediction and provide a rationale for evaluating the performance of the reward task at two time points (1 week apart) in HC participants.

Methods: Forty control participants were tested twice, one week apart, in one of four sites (10 participants per site). Three participants were excluded—one due to a missing time 1 scan, one due to severe ghosting, and one due to a very low signal to noise ratio (SNR: 41). All included individuals had SNR of >80. All participants performed a reward-related guessing task. Following previous studies, two main contrasts were evaluated using parametric modulators: a regressor reflecting signed prediction errors (PE) and a regressor reflecting reward expectancy (RE). A functionally-defined mask of the ventral striatum (VS) was obtained from a previous study with the same task (identifying activity coupled to PEs) and used for region of interest analysis. We report data for the right VS, but similar findings were observed on the left. As a positive control, we used another contrast from the same task unrelated to reward processing (anticipation *per se*), and extracted from bilateral visual cortex.

Results: Significant VS PE-related activity was observed at time 1 ($t=5.65$, $p<0.001$) but not time 2 ($t=1.50$, $p=0.14$), and the magnitude of reduction was significant ($t=3.060$, $p=0.004$). Conversely, significant VS RE-related activity was observed at time 2 ($t=2.74$, $p=0.009$) but not time 1 ($t<1$). Moreover, across participants, increases in VS RE-related activity from time 1 to time 2 were associated with decreases in VS PE-related activity from time 1 to time 2 across participants ($r=-0.39$, $p=0.016$). ICCs in VS were very low (RE: 0.20; PE: 0.00), and no significant correlations between time 1 and time 2 were observed (p's >0.2). Despite large differences in overall activation in the visual cortex from time 1 to time 2 (t's >3.47, $p<0.002$), ICCs to the anticipation *per se* contrast were higher (left 0.52; right 0.36), and activity in this region was significantly correlated between time 1 and time 2 (r's >0.37, $p<0.025$).

Conclusions: Dynamic changes in brain activation are widely predicted by a variety of psychological theories. Nevertheless, conventional measures of reliability (e.g. ICCs) cannot distinguish between lawful, dynamic changes and noisy signal. In the present work, we provide evidence for the former of the two possibilities: reward-related VS activation has very low ICCs, yet clearly follows the pattern predicted by temporal difference models of reward learning. These models hold that following conditioning, reward-related activation should move to the earliest predictor of reward. Thus we observed significant prediction VS-error related activation coupled to the outcome diminish from time 1 to time 2, whereas VS-reward expectancy related activation coupled to a predictive cue was observed to increase. These findings have implications for psychopharmacological studies in individuals with depression and the development of reward-related biomarkers: namely that effective planning of longitudinal studies of reward-related neural circuits systems must incorporate their known dynamics.

Keywords: Reliability, neuroimaing, biomarker, reward, depression

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M60. Increased Serotonin Transporter Binding Is Associated with Depression Development during Interferon-alpha Exposure in Humans

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Background: Cross-sectional positron emission tomography (PET) studies of the serotonin transporter (5-HTT) indicate that levels may be increased in subjects with major depression (MD), but this has not been consistently replicated. Prospective studies of rodents do demonstrate that stress-related increases in 5-HTT are greater in rats bred for high anxiety than those with low anxiety. To prospectively examine the role of 5-HTT in humans, we recruited euthymic subjects who would be soon initiating interferon-alpha (IFN-α) therapy – to examine whether changes in 5-HTT could be prospectively associated with depression development. IFN-α is an inflammatory cytokine that is capable of triggering an episode of MD in about 33% of people within months, and IFN-α can increase expression of 5-HTT in cell cultures in vitro. It was hypothesized that exogenous IFN-α administration could increase 5-HTT expression in humans, thereby increasing the likelihood of developing MD.
Methods: We recruited seven euthymic adult subjects patients with hepatitis C but who were otherwise generally physically healthy (Cumulative Illness Rating Scale-Geriatric score <5), without a current axis I mood, psychosis, anxiety, or substance use or taking an antidepressant, mood stabilizer, or antipsychotic medication. PET images were obtained prior to starting IFN-a therapy and then again 3–4 weeks into treatment. Data were acquired in the 3D mode for 90 min following injection of [^{11}C]DASB, which is selective for 5-HTT. MRI and PET scans were co-registered to allow drawing of anatomical regions of interest (ROIs), and time-activity curves were derived for one-tissue compartmental analysis. [^{11}C]DASB BP_{ND} was derived as the difference between the ROI and cerebellum, normalized to the cerebellum. We focused on the whole medial temporal lobe. Depression diagnosis was confirmed by a mood-specific SCID-IV interview, and quantified with the Beck Depression Inventory and Montgomery Asperg Depression Rating Scale.
Results: Of the 57% of subjects who did not develop MD, all had decreases in [^{11}C]DASB BP_{ND} in the medial temporal lobes during IFN-a therapy. Of the 43% of subjects developed MD, all had increases in [^{11}C]DASB BP_{ND} in the medial temporal lobes. There were no differences in baseline 5-HTT binding comparing those who develop MD *vs* those who did not. One subject deferred starting therapy.
Conclusions: This is preliminary evidence that temporal lobe 5-HTT binding can either increase or decrease in different people during IFN-α therapy. 5-HTT levels prior to IFN-α therapy were not predictive of vulnerability, but rather changes in 5-HTT were correlated with depression development. Supporting the hypothesis, increased 5-HTT was strongly associated with the development of MD. Although IFN-α can influence a number of systems ranging from glutamate to dopamine, these results supporting the likely involvement of increased 5-HTT levels in MD's etiology.
Keywords: mood disorder, cytokine, inflammation, serotonin, PET, neuroimaging, prospective
Disclosures: F. Lotrich, Nothing to Disclose; R. Narendran, Nothing to Disclose.

M61. Naloxone-Reversible Modulation of Pain Circuitry by Left Prefrontal Repetitive Transcranial Magnetic Stimulation

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Background: A 20-min session of 10 Hz repetitive transcranial magnetic stimulation (rTMS) of Brodmann Area (BA) 9 of the left dorsolateral prefrontal cortex (DLPFC) can produce analgesic effects on postoperative and laboratory-induced pain. This analgesia is blocked by pretreatment with naloxone, a μ-opioid antagonist. The purpose of this sham controlled, double blind, crossover study was to identify the neural circuitry that underlies the analgesic effects of left DLPFC rTMS and to examine how the function of this circuit, including midbrain and medulla, changes during opioid blockade.
Methods: Fourteen healthy volunteers were randomized to receive intravenous saline or naloxone immediately prior to sham and real left DLPFC rTMS on the same experimental visit. One week later, each participant received the novel pretreatment but the same stimulation paradigm. Using short sessions of heat on capsaicin-sensitized skin, hot allodynia was assessed during 3 T functional magnetic resonance imaging (fMRI) scanning at baseline, post-sham rTMS, and post-real rTMS. Data were analyzed using whole-brain voxel-based analysis as well as time series extractions from anatomically defined regions of interest representing midbrain and medulla.
Results: Consistent with previous findings, real rTMS significantly reduced hot allodynia ratings. This analgesia was associated with elevated BOLD signal in DLPFC and diminished BOLD signal in the anterior cingulate, thalamus, midbrain and medulla during pain. Naloxone pretreatment largely abolished rTMS-induced analgesia as well as rTMS-induced attenuation of BOLD signal response to painful stimuli throughout pain processing regions, including midbrain and medulla.
Conclusions: These preliminary results suggest that left DLPFC rTMS drives top-down opioidergic analgesia.
Keywords: Pain, rTMS, endogenous opioids, analgesia, prefrontal cortex
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M62. Abnormalities of Two Distributed Brain Networks in Major Depression

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Background: Mood disorders involve disturbances in multiple brain functions—such as mood, pleasure, motivation, and cognition—which are supported by different large-scale brain networks. Traditional univariate analyses have revealed abnormalities in specific brain *regions*, but the brain *networks* that are disturbed remain unclear. We used a multivariate approach to identify functional brain network abnormalities in major depressive disorder (MDD).
Methods: Participants silently viewed emotional words during functional magnetic resonance imaging (fMRI). Independent component analysis (ICA) was implemented with the Group ICA of fMRI Toolbox. Activation of each component (i.e., network) was computed by correlating each component time course with the modeled task effect. Group differences in activation were tested in 51 healthy control women, 12 women with MDD, and 15 women with borderline personality disorder (BPD).
Results: We identified 23 distinct functional networks, about half of which were activated by the task. Two networks showed significant group differences in activation ($p < 0.05$, corrected). Control and BPD subjects deactivated both networks during word presentation, whereas MDD subjects activated both networks. The subgenual cingulate cortex was the only region shared by the two networks.
Conclusions: Our findings suggest that MDD is associated with abnormal engagement of two distinct functional brain networks that share a node in the subgenual cingulate cortex. This abnormality may be specific to MDD, since normal deactivation was observed in the BPD group. These results deserve to be replicated in a larger sample.
Keywords: major depressive disorder, independent component analysis, network, subgenual cingulate, borderline personality
Disclosures: A. Petti, Nothing to Disclose; D. Kessler, Nothing to Disclose; M. Heitzeg, Nothing to Disclose; S. Langenecker, Nothing to Disclose; T. Love, Nothing to Disclose; K. Silk, **Part 1:** Alkermes - Single day consultancy; J. Zubieta, ; C. Sripada, Nothing to Disclose; B. Mickey, Nothing to Disclose.

M63. Contrasting Gray Matter Volume Biomarkers by Diagnosis and Biotype across Schizophrenia - Bipolar Disorder Psychosis Dimension

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Background: Categorization of psychotic disorders is based entirely on clinical phenomenology and lucks underlying biological definitions. Resulting diagnoses [e.g., schizophrenia (SZ) or bipolar disorder (BD)] show substantial clinical heterogeneity and do not align with emerging biomarker constructs. One of the strategies that seeks to identify valid disease biomarkers and subsequently develop neurobiologically-derived grouping of psychosis is taxometric multivariate analyses carried out across the entire dimension of psychosis cases independent of categorical diagnoses. Based on this approach, we contrast gray matter volume biomarkers across two alternative disease constructs: DSM-IV diagnoses vs. biotypes, the psychosis groups derived from cognitive and sensorimotor biomarkers analyses.
Methods: *The diagnosis analysis* included 351 psychosis probands [146 with SZ (SZP), 90 with schizoaffective disorder (SADP), and 115 with psychotic BD, type I (BDP)], 369 of their first-degree relatives [134 SZR, 106 SADR, 129 BDR], and 200 healthy controls (HC) from Bipolar-Schizophrenia Network in Intermediate Phenotypes (B-SNIP) sample. *The biotype analysis* included 338

probands [81 biotype 1, 114 biotype 2, 143 biotype 3] and 265 relatives [62 biotype 1, 81 biotype 2, 122 biotype 3], contrasted with 200 HC. The biotype groups were derived from the pool of the psychosis probands using a series of step-wise multivariate analyses (PCA, unsupervised cluster analysis, canonical discriminant analysis) of cognitive (BACS), eye movement (antisaccade/prosaccade task) and EEG-based paired auditory stimuli ERP measures. Gray matter volume characteristics from 3 Tesla T1-weighted MPRAGE images analyzed with SPM8/VBM8/DARTEL are contrasted by diagnosis vs. biotypes.
Results: *The diagnosis analysis* showed extensive and overlapping gray matter volume reductions in numerous cortical and subcortical regions in SZP and SADP, compared to HC. In contrast, BDP showed largely normal cortical/subcortical gray matter, with small clusters of reduction in fronto-temporal, cingulate, and insular cortices. No volume differences were observed in any relative group compared to HC. *The biotype analysis* revealed diffuse cortical and subcortical gray matter reductions in biotype 1 probands, the most impaired biotype based on cognitive and sensorimotor characteristics; lesser gray matter volume reductions in biotype 2 characterized by impaired cognitive function and exaggerated sensorimotor reactivity; and minimal volume reductions localized to fronto-temporal, cingulate, and insular regions in biotype 3 consistent with near normal cognitive and sensorimotor function, compared to HC. Biotype 1 relatives showed gray matter volume reductions regionally overlapping but lesser in magnitude than those in probands, whereas biotype 2 and 3 relatives had normal gray matter volume, compared to HC. SZ, SAD, and BD diagnoses were distributed across the three biotypes with a relative predominance of SZ cases in biotype 1 (59% SZP, 23% SADP, 17% BDP) and biotype 2 (42% SZP, 29% SADP, 29% BDP), and BD cases, in biotype 3 (31% SZP, 23% SADP, 46% BDP).
Conclusions: Our findings support partially divergent anatomic brain structure biomarkers for SZ/SAD (i.e., diffuse cortical and subcortical gray matter volume loss) and psychotic BD (i.e., smaller localized volume reductions in fronto-temporal and anterior limbic regions), as well as normal gray matter characteristics in relatives. Re-slicing this psychosis sample by biotype captures more homogenous groups of proband and relative cases characterized by consistent cognitive, sensorimotor, and gray matter structure biomarkers, largely independent of clinical diagnostic definitions. Psychosis subgroups defined by biomarker, not phenomenological, characteristics may better predict etiology, pathophysiology, biomarker heritability, and treatment response.
Keywords: schizophrenia, bipolar disorder, psychosis, endophenotypes, VBM
Disclosures: E. Ivleva, **Part 4:** MH077851, The National Institute of Mental Health ; A. Bidesi , **Part 4:** MH077851, The National Institute of Mental Health ; B. Clementz, Nothing to Disclose; M. Keshavan, **Part 4:** MH078113, The National Institute of Mental Health ; S. Meda, **Part 4:** MH077945, The National Institute of Mental Health ; G. Pearlson, **Part 4:** MH077945, The National Institute of Mental Health ; J. Sweeney, **Part 4:** MH077862, The National Institute of Mental Health ; G. Thaker, **Part 4:** MH077852, The National Institute of Mental Health ; C. Tamminga, **Part 4:** MH077851, The National Institute of Mental Health

M64. Neuroimaging Abnormalities in Borderline Personality Disorder: MRI, MRS, fMRI and DTI Findings

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Background: Borderline personality disorder (BPD) is a serious neuropsychiatric illness characterized by disturbance of affect, impulsivity, unstable relationships and altered self-image. Although it is diagnosed on the basis of clinical features and has been conceptualized as having a psychological etiology, there is growing literature suggesting structural and functional brain changes are also a part of the pathology. Imaging modalities have elucidated variation in structure (via MRI), function (fMRI), spectroscopic analyses (MRS), and white matter tractography (DTI). Here, we review the extensive literature of the controlled neuroimaging studies in BPD and discuss their relevance.
Methods: We reviewed the English literature using PubMed and keywords 'borderline personality' , 'neuroimaging' , 'MRI' , 'MRS', 'fMRI', and 'DTI'. 37 articles met criteria for inclusion (studies performed using control group). Articles were classified into four types of neuroimaging – structural, functional, spectroscopic and white matter tractography-—and the findings tabulated.
Results: Compared to control groups, neuroimaging findings included: 1. Structural imaging: 16 of 21 studies found differences from controls including significant decreases in volume of hippocampus, amygdala, frontal/temporal/parietal cortices. 2. Spectroscopic: 4 of 5 studies reported neurotransmitter variations amongst BPD patients including increased glutamate concentration in anterior cingulate cortex, increased serotonin transmitter availability in brainstem and hypothalamus as well as decreased N-acetylaspartate in amygdala and dorsolateral prefrontal cortex. 3. fMRI : 8 of 8 studies positive for differences in connectivity/activation/metabolism in various regions including amygdala, frontopolar cortex, insula, anterior cingulate cortex. 4. White matter: 3 of 3 DTI studies detected abnormalities in inferior longitudinal/uncinate/occipital fasciculi, corpus callosum, and hemispheric connectivity compared to matched controls.
Conclusions: Cumulatively, these findings represent a strong body of evidence for BPD as a disorder of brain structure and function, and of both gray and white matter. These loci of neurological changes provide not only potential biomarkers but also potential etiology/pathogenesis clues. Given the role of early trauma in BPD as well as the genetic transmission of BPD, these findings may represent a gene-by-environment (GXE) interaction in BPD.
Keywords: Borderline personality, neuroimaging, MRI, fMRI, DTI
Disclosures: C. McKenzie, Nothing to Disclose; H. Nasrallah, **Part 1:** Gruenthal, Boehringer-Ingelheim, Genentech, Janssen, Merck, Lundbeck, Novartis, Otsuka, Roche, Shire, Sunovion, **Part 2:** Janssen, Merck, Novartis, Sunovion, **Part 3:** Janssen, Merck, Novartis, Sunovion, **Part 4:** Lilly, Shire,

Otsuka, and Roche. All provided research grants through my university.

M65. Cerebral Blood Flow Differences in Major Depressive Disorder using Arterial Spin Labeling: Preliminary Results from the EMBARC Study

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Background: Arterial spin labeling (ASL) is a noninvasive neuroimaging technique used to measure cerebral blood flow (CBF; i.e., perfusion) and could be used as an effective tool to understand resting state abnormalities in patient populations such as major depressive disorder (MDD). So far, previous research using ASL in depression revealed CBF abnormalities in the default mode network in some cases (Orosz *et al*, 2012). ASL has also been observed to accurately classify unipolar from bipolar depression based on differences in CBF of the anterior cingulate cortex (ACC; Almeida *et al*, 2013). Given these findings, ASL could become a prospective biomarker of disease state as well as treatment choice and monitoring in the clinical setting with more research. The EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) study is a nation-wide randomized control trial investigating such biomarkers in MDD. ASL is being investigated in order identify differences in CBF between patients with MDD and healthy controls.
Methods: Participants consist of 40 healthy controls and 100 patients with MDD before starting medication. All participants were scanned in one of four sites, and underwent 3 T MRI scanning, which included an ASL scan that used pseudo-continuous labeling, i.e. PCASL, and lasted approximately 6 min. CBF was compared between the healthy control and MDD groups using a whole-brain voxel-by-voxel analysis.
Results: Preliminary results show several regions of interest to be significantly different between the two groups. These include regions such as the ACC, insula cortex, and caudate. Clusters in these regions were significant at $t = 3.21$; $p < 0.001$; with at least 50 continuous voxels set at the extent threshold. Patients with MDD were observed to have reduced perfusion in the ACC, insula, and caudate relative to healthy controls.
Conclusions: While ASL has been more widely used as a research tool, it has the prospects of being used as a tool for clinical diagnostics and informing treatment decisions. Our present work provides further evidence to the role of ASL in detecting abnormalities in resting CBF for multiple brain regions including those that are implicated in the default mode network as well as other regions thought to be important in the phenotype of MDD. These preliminary results may have implications for future studies aimed at further developing CBF as a biomarker in clinical populations. In this regard, the final sample of the EMBARC study, which will include roughly 400 patients with MDD and their outcomes data, will provide evidence for the application of CBF to predict treatment outcomes in MDD.
Keywords: Arterial Spin Labeling Cerebral Blood Flow Major Depressive Disorder Biomarkers
Disclosures: C. Cooper, Nothing to Disclose; H. Lu, Nothing to Disclose; J. Almeida, Nothing to Disclose; H. Chase, Nothing to Disclose; T. Carmody, Nothing to Disclose; M. Fava, **Part 2:** Dr. Fava has copyrights for the Sexual Functioning Inventory (SFI) and the Antidepressant Treatment Response Questionnaire (ATRQ).; T. Jin, Nothing to Disclose; B. Kurian, Nothing to Disclose; P. McGrath, Nothing to Disclose; M. McInnis, Nothing to Disclose; M. Oquendo; R. Parsey, Nothing to Disclose; M. Weissman, Nothing to Disclose; S. Weyandt, Nothing to Disclose; M. Phillips, Nothing to Disclose; M. Trivedi, Nothing to Disclose.

M66. Exposure to Regional Anesthesia during Labor and Delivery and Its Effect on Neonatal Brain Morphology

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Background: Recent animal and human epidemiological studies suggest that early exposure to anesthesia have adverse effects on brain development. As more than 50% of pregnant women in the United States receive regional anesthesia during labor and delivery, understanding the effects of anesthesia on brain development is of high public health relevance. We used MRI to assess the effects of anesthesia during labor and delivery.
Methods: Using high-resolution MRI, we mapped morphological features of the cortical surface and brain parenchyma in 37 healthy neonates, 24 exposed and 13 unexposed to regional anesthesia.
Results: Neonates exposed to maternal anesthesia compared with unexposed neonates had enlarged frontal and occipital lobes, and right posterior portion of the cingulate gyrus, as well as reduced thalamus and basal ganglia volumes. Longer durations of exposure to anesthesia correlated positively with surface measures in the occipital lobe, and inversely with thalamus and basal ganglia volumes. The correlations of surface measures with postmenstrual age as an index of brain maturation were similar in both exposure groups and included enlargement of the frontal and occipital lobes bilaterally. This correlation was more pronounced in the infants exposed to anesthesia, and was located in the same regions where anesthesia-related enlargement was most significant.
Conclusions: These findings are consistent with those from animal studies that demonstrate alterations in cellular and molecular processes as a consequence of anesthetic exposure during labor and delivery. Longitudinal MRI studies are needed to determine whether these morphological effects of anesthesia persist and what their consequences on cognition and behavior may be.

Keywords: Neonate Brain Morphology Anesthesia Maternal Labor and Delivery
Disclosures: M. Spann, Nothing to Disclose; R. Bansal, Nothing to Disclose; T. Rosen, Nothing to Disclose; B. Peterson, Nothing to Disclose.

M67. Abnormal Deactivation of Ventrolateral Prefrontal Cortex during Emotion Processing in Youth with Bipolar Disorder: Effects of Medication and Mood State

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Background: Bipolar disorder (BD) in youth has been associated with abnormalities in activation of prefrontal areas and amygdala during emotion processing tasks. While medications have a normalizing effect (attenuating observed differences between BD youth and healthy controls), studies comparing medicated and non-medicated youth are limited. Using data from the Longitudinal Assessment of Manic Symptoms Cohort (a multi-site clinical sample recruited for behavioral and emotional dysregulation), we examined the joint impact of BD and medication on activation in these regions.
Methods: BOLD fMRI data were obtained from 15 youth with unmedicated BD (U-BD), 19 youth with medicated BD (M-BD), a non-bipolar clinical sample (non-BD, $n = 59$) and 29 healthy controls (HC) while they were shown task-irrelevant morphing emotional faces and shapes. The mean age of the participants at time of scan was 13.7 (+ 2.1) years old, and 57% were male. Groups did not differ significantly according to age, gender, IQ, or socioeconomic status (as measured by parental college education). Because our hypotheses focused on circuitry involved in emotional processing, we constructed a one-way ANOVA in SPM8 to assess group differences across a region of interest that included the amygdala, orbitofrontal cortex (BA 11), ventrolateral prefrontal cortex (VLPFC, BA 47), and anterior cingulate cortex. The fMRI data (for the emotions vs. shapes contrast) were extracted from voxels that showed significant group differences in both unadjusted and covariate-adjusted (site, age, gender, and IQ) models, indicating that they were robust to confounding. To correct for multiple comparisons, only clusters that exceeded a threshold of 112 voxels (based on a Monte Carlo simulation to maintain a two-sided alpha of .05) were extracted. Pairwise group comparisons, the impact of other diagnoses and mood state, and the effects of specific emotional stimuli on mean cluster activation were further assessed in SAS 9.2 using PROC GLM.
Results: Compared to morphing shapes, emotional faces increased BOLD signal in the bilateral amygdala across groups (corrected $p < 0.05$); bilateral VLPFC activation was also observed in the HC and non-BD, but not the youth with BD. A single cluster in the right VLPFC showed group differences to emotion vs. shapes (137 voxels, corrected $p < 0.05$). Compared to HC and non-BD youth, U-BD youth showed decreased activity in this cluster ($p = 0.005$). M-BD also showed decreased activity in this cluster relative to HC ($p = 0.02$) and non-BD youth ($p = 0.03$), but these differences were attenuated. Other diagnoses (attention-deficit hyperactivity disorder and disruptive behavioral disorders) did not impact cluster activation, and adjustment for these variables did not impact the effect of group. Depressive symptoms were positively correlated with cluster activation ($p = 0.015$), while manic symptoms were negatively correlated (within the bipolar sample) ($p = 0.015$). Significant group differences were found in response to all negative emotions (fear, sadness, and anger), but not happy faces.
Conclusions: As compared to both HC and a non-BD sample, BD (especially unmedicated) was associated with abnormally decreased right VLPFC activation to negative emotions, which was even more pronounced in youth with manic symptoms at time of scan. These results support the hypotheses that youth with bipolar disorder show abnormalities in emotion regulation circuitry, which are attenuated by medication and are not present in a non-bipolar clinical sample. The VLPFC is emerging as a region that, given its role in emotion regulation, is potentially important for the pathophysiology of BD. Previous work has shown that BD in adults was associated with decreased activation in this region relative to healthy controls and adults with major depressive disorder. Additionally, decreased activation of this region has been correlated with manic symptomatology, and has been shown to normalize with treatment in youth with BD. Thus the current results build on a body of work that highlights the possible role of VLPFC deactivation in bipolar disorder, and identify this region as a potential biomarker for further investigation.
Keywords: fMRI bipolar disorder ventrolateral prefrontal cortex child psychiatry medication effects
Disclosures: D. Hafeman, Nothing to Disclose; G. Bebko, Nothing to Disclose; M. Bertocci, Nothing to Disclose; L. Bonar, Nothing to Disclose; S. Perlman, Nothing to Disclose; V. Diwadkar, Nothing to Disclose; R. Kowatch, **Part 1:** REACH, Astra-Zeneca and Sunovion; B. Birmaher, Nothing to Disclose; S. Horwitz, Nothing to Disclose; E. Arnold, Nothing to Disclose; M. Fristad, Nothing to Disclose; E. Youngstrom, Nothing to Disclose; R. Findling, **Part 1:** Alexza Pharmaceuticals, American Psychiatric Press, AstraZeneca, Bracket, Bristol-Myers Squibb, Clinsys, Cognition Group, Forest, GlaxoSmithKline, Guilford Press, Johns Hopkins University Press, Johnson & Johnson, KemPharm, Lilly, Lundbeck, Merck, NIH, Novartis, Noven, Otsuka, Oxford University Press, Pfizer, Physicians Postgraduate Press, Rhodes Pharmaceuticals, Roche, Sage, Seaside Pharmaceuticals, Shire, Stanley Medical Research Institute, Sunovion, Supernus Pharmaceuticals, Transcept Pharmaceuticals, Validus, and WebMD. , **Part 2:** Guilford Press, Shire, WebMD, **Part 4:** AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, Lilly, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Rhodes Pharmaceuticals, Roche, Shire, Sunovion, Supernus Pharmaceuticals.; T. Frazier, Nothing to Disclose; W. Drevets, **Part 5:** Janssen Pharmaceuticals of Johnson & Johnson, ; M. Phillips, Nothing to Disclose.

M68. Kappa Opioid Receptor Systems and Threat, Loss, and Reward Responsiveness

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Background: Accumulating evidence suggests that theactivated dynorphin/kappa opioid receptor (KOR) system is implicated in the etiology of negative valence systems implicated in acute threat (i.e., fear), potential threat (i.e., anxiety), and sustained threat; and loss (i.e., anhedonia), as well as positive valence systems implicated in sustained/longer-term responsiveness to reward attainment.
Methods: Using the KOR-selective radioligand [^{11}C]LY2795050 and positron emission tomography (PET), we studied *in vivo* the role of KOR systems in relation to the phenotypic expression of threat and loss symptomatology, and reward responsiveness. We employed a stratified, transdiagnostic/symptom-based recruitment approach to study $n = 22$ individuals between the age of 18 to 55, whose symptom levels as assessed by the MADRS covered the full dimensional spectrum of threat- and loss-related symptomology, ranging from asymptomatic healthy participants ($N = 11$) to individuals with elevated depressive symptomatology ranging from mild to severe ($N = 11$). We chose to use V_T as our primary outcome measure of KOR brain availability.
Results: A multivariate ANOVA with group status (HC vs. Elevated threat and loss symptom), sex, and Elevated threat and loss symptom status x sex interaction entered as independent factors, and [^{11}C]LY2795050 scores in the ventral striatum and striatum entered as the dependent variables revealed a significant main effect of Elevated threat and loss symptom group status ($F(2,17) = 5.84$, $p = 0.012$), with the Elevated threat and loss symptom group having significantly lower [^{11}C]LY2795050 values in the ventral striatum (Cohen's $d = 1.56$, 95%CI = 0.61–2.52) and amygdala (Cohen's $d = 1.42$, 95%CI = 0.48–2.35) compared the HC group. [^{11}C]LY2795050 values in the ventral striatum were differentially negatively associated with severity of dysphoria/anhedonia symptoms ($\beta = -0.57$, $t = 3.07$, $p = 0.006$; adjusted $R^2 = 0.29$); and [^{11}C]LY2795050 values in the amygdala were differentially negatively associated with severity of anxiety symptoms ($\beta = -0.49$, $t = 2.50$, $p = 0.021$; adjusted $R^2 = 0.20$). Inspection of [^{11}C]LY2795050 values in the ventral striatum and amygdala between women ($n = 7$) and men ($n = 4$) with elevated threat and loss symptoms revealed that women had significantly lower [^{11}C]LY2795050 values in the ventral striatum ($t(9) = 3.23$, $p = 0.010$, Cohen's $d = 2.03$, 95%CI = 0.53–3.52), and marginally lower [^{11}C]LY2795050 values in the amygdala ($t(9) = 2.00$, $p = 0.076$, Cohen's $d = 1.25$, 95%CI = 0.09–2.58).
Conclusions: These data provide strong evidence for regional neural specificity of association between reduced KOR availability in the ventral striatum and elevated loss (i.e., anhedonic) symptoms and decreased reward responsiveness and between reduced KOR availability in the amygdala and elevated threat (i.e., anxiety) symptoms.
Keywords: Kappa opioid receptor systems, positron emission tomography, RDoC.

Disclosures: R. Pietrzak, Nothing to Disclose; Y. Huang, Nothing to Disclose; M. Naganawa, Nothing to Disclose; S. Corsi-Travali, Nothing to Disclose; R. Carson, Nothing to Disclose; A. Neumeister, **Part 4:** Eli Lilly, Inc.

M69. Pallidial Resting State Connectivity in Bipolar Disorder: Implications for Differences between Manic and Depressive States

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Background: The nature and location of the pathological processes responsible for the switch between mania and depression in bipolar disorder remains to be elucidated. The anterior cingulate cortex-striato-pallidial-thalamic-cortical circuit has been implicated as the mood regulating circuit (MRC). In this study we investigated the resting state connectivity ventral striatum (VST), ventral palladium (VP), dorsomedial thalamus (DMTHAL) and anterior cingulate cortex (ACC) in manic and depressed bipolar patients.
Methods: Unmedicated depressed and manic bipolar BDD and matched healthy controls underwent functional magnetic resonance imaging (fMRI) imaging. In each session, a resting state connectivity scan was obtained. ROI time series was extracted from seed regions and correlations of low frequency BOLD fluctuations (LFBF) were calculated.
Results: In this ongoing study we have analyzed data from 30 bipolar depressed (Age: 34.7 + 11.5;18F), 30 manic subjects (Age: 34.5 + 11.9 ; 18F), and 30 matched healthy subjects (Age: 31 + 9.1; 18F). Significant group main effects were investigated with post-hoc t tests. Compared to healthy subjects, the depressed group exhibited increased connectivity of DMTHAL with VP on the left side. The manic group exhibited decreased connectivity of ACC with VP on the left side.
Conclusions: This preliminary analysis suggests that manic and depressive states in bipolar disorder may be associated with changes in connectivity of the ventral palladium with other components of the MRC.
Keywords: Bipolar disorder, resting state connectivity, mania, depression, pallidium, thalamus, striatum, cingulate cortex, mood circuit.
Disclosures: A. Anand, Nothing to Disclose; H. Karne, Nothing to Disclose.

M70. Hippocampus NAA as Biological Marker of Anhedonia in PTSD and Trauma-exposed Adults: Preliminary 1H-MRS Findings

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Background: Hippocampus morphological alterations have been implicated in the pathogenesis of post-traumatic stress disorder (PTSD), and may be related to neuronal injury sub-

sequent traumatic events. In animal models of stress and trauma, markers of hippocampal neuronal loss and excitotoxicity have been associated with the presence and degree of anhedonia, a phenotype that translates to multiple clinical diagnostic phenotypes, including PTSD and major depressive disorder (MDD). The current study used proton magnetic resonance spectroscopy (^{1}H-MRS) in the hippocampus of adults with PTSD, trauma-exposed healthy adults, and nontraumatized healthy adults. We hypothesized that presence and degree of anhedonia would be associated with ^{1}H-MRS measures of hippocampus neuronal integrity and glutamate metabolism.

Methods: ^{1}H-MRS neurochemical data were acquired from the right and left hippocampi of 20 PTSD and 18 healthy control (10 trauma-exposed) subjects using a 4 Tesla MR scanner. All subjects received semi-structured psychiatric interviews and completed self-report measures of mood, including the Beck Depression Inventory, second edition (BDI). Anhedonia was defined both as a categorical variable (present, absent) and as a quantitative score based on relevant BDI items. Hippocampus glutamate and NAA levels were quantified relative to unsuppressed water.

Results: Compared with healthy subjects, PTSD patients had significantly lower NAA/H20 ($t = 2.58$, $p = 0.01$) and significantly higher glutamate/H20 ($t = 3.21$, $p < 0.003$) in the right hippocampus. When the PTSD group was subdivided based on the presence of anhedonia, only anhedonic patients had significantly reduced right hippocampus NAA/H20 ($t = 9.16$, $p < 0.001$; p(Tukey) $< .01$). Moreover, in the sample as a whole, presence of anhedonia was associated with significantly lower right hippocampus NAA/H20, and anhedonia scores were significantly negatively correlated with right hippocampus NAA/H20 ($r_s = -0.41$, $p = 0.01$).

Conclusions: Our pattern of results indicates that hippocampus NAA reductions are a neural correlate of anhedonia in PTSD, and also irrespective of PTSD diagnosis in a mixed sample of trauma-exposed and nontraumatized adults. Diminished positive affectivity or reward functioning is a prominent yet understudied component of PTSD phenomenology, and contributes to elevated comorbidity of PTSD with other clinical disorders such as MDD. Altogether our findings encourage further inquiry into hippocampus NAA as a possible neural underpinning of anhedonia across DSM-V categories, and as a construct of relevance to the diagnostically agnostic NIMH RDoC dimensional system.

Keywords: posttraumatic stress disorder, magnetic resonance spectroscopy, n-acetylaspartate, anhedonia, biomarkers

Disclosures: I. Rosso, Nothing to Disclose; D. Crowley, Nothing to Disclose; L. Preer, Nothing to Disclose; M. Silveri, Nothing to Disclose; J. Jensen, Nothing to Disclose.

M71 Equal HIV Risk Reduction with Buprenorphine-Naloxone or Methadone

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Background: To compare reductions in HIV injection and sexual risk behaviors in patients receiving maintenance treatment with methadone (MET) or buprenorphine/Naloxone (BUP).

Methods: We used data from a previously randomized trial that evaluated transaminase differences in patients receiving MET or BUP. The Risk Behavior Survey (RBS) measured past 30-day HIV risk behaviors at baseline and at weeks 12 and 24. Participants were consenting, treatment seeking, opioid-dependent individuals who were starting a new treatment episode, remained in their assigned condition for 24 weeks, and had 4 or more blood draws across the treatment period.

Results: The results showed that among the 731 participants who stayed in treatment for 24 weeks (BUP = 340; MEt = 391), 700 completed a 12-week RBS assessment, and 705 completed the 24-week RBS. Highly significant reductions in injecting risk ($p < 0.0001$ to 0.0008) were seen across time with no differences between groups in mean number of times participants reported injecting heroin, speedball, and other opiates, total number of injections, the percent who shared needles and did not clean shared needles with bleach, shared cookers, and engaged in front/back loading. Other significant ($p < 0.03$–0.05) reductions were reported in the percentage of participants having more than one sex partner. MET participants reported a significant reduction in unsafe sex behaviors (0.05), and also a greater reduction in a sex risk composite score than BUP participants ($p < 0.04$).

Conclusions: HIV injecting risk behaviors were equally and markedly reduced in those who remained on MET or BUP over the 24-week treatment. Significant, but less dramatic reductions were seen in sex risk behaviors, with greater reduction in MET than BUP participants.

Keywords: HIV Risk Reduction; Buprenorphine-Naloxone; Methadone

Disclosures: G. Woody, Nothing to Disclose; D. Bruce, Nothing to Disclose; P. Korthuis, Nothing to Disclose; S. Chhatre, Nothing to Disclose; M. Hillhouse, Nothing to Disclose; J. Sorensen, Nothing to Disclose; A. Saxon, **Part 1:** Alkermes Inc Scientific Advisory Board, Reckitt Benckiser Inc. speaker; P. Jacobs, Nothing to Disclose; D. Metzger, Nothing to Disclose; S. Poole, Nothing to Disclose; W. Ling, **Part 1:** Reckitt Benckiser Research support, consultant, Titan Pharmaceuticals travel support, Alkermes: research medication support.

M72. Excellent Test-retest Reliability of Cerebral Blood Flow in Healthy Individuals Measured with Arterial Spin Labeling: EMBARC Study Preliminary Results

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Background: Cerebral blood flow (CBF) at rest is a widely used method of examining baseline states in both healthy

individuals and those with neurological or psychiatric disorders. Most of the studies measuring CBF used invasive technologies, due radioligands, to measure CBF, such as, positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Arterial spin labeling (ASL) is a magnetic resonance imaging technology to measure CBF using endogenous water as a tracer and, therefore, ASL is non-invasive technique. ASL has being used to measure blood flow in different areas of the body (e.g. lungs and kidney) for more than two decades. Only recently ASL was applied to study CBF in healthy and psychiatric populations. The simplicity of the MRI protocol, and the strength and reliability of emerging analysis makes it a promising avenue for the development of biomarkers to examine longitudinal changes during the treatment process. Previous investigations of the test-retest reliability of resting ASL have generally revealed an optimistic picture. In the present study, we seek to add to this literature and compare test-retest reliability across experimental sessions in a group of healthy control individuals using data from EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care). EMBARC studay is a nation-wide randomized control trial investigating biomarkers in depression. We will examine test-retest reliability within relative mean cerebral blood flow in regions of interest (default mode network, salience network). We hypothesize that intraclass correlations (ICC) will be around 0.6–0.8. Furthermore, we will examine the effect of site on the cerebral blood flow measures within these regions.

Methods: We measured cerebral blood flow in thirty healthy controls in two different scan sessions one week apart in three different experimental sites. University of Texas Southwestern and University of Michigan used a Philips scanner, while Massachusetts General Hospital used a Siemens scanner. All scanners were 3 Tesla. Pseudo-continuos arterial spin labeling protocols were maximized to achieve best balance between performance, and quality while maintaining similar parameters. Data was processed using SPM5 and cerebral blood flow was derived from arterial spin labeling images with an automated algorithm. Regions of interest for the default mode and salience network included: bilateral ventrolateral and dorsolateral, ventromedial, dorsomedial prefrontal cortex, bilateral amygdala, bilateral insula, anterior and posterior cingulate cortex and bilateral ventral striatum. ICCs were calculated using IBM SPSSv21. Cronbach's Alpha was considered poor if lower then 0.40, fair if between 0.40 and 0.58, good if between 0.59 and 0.75, and excellent if greater than 0.75. Effect of site was investigated using a 2 (session) by 3 (site) repeated measures anova.

Results: All Cronbach's Alpha measures were good or excellent with the exception of one region that had a poor ICC. The highest alpha was associated with the anterior cingulate cortex (0.9) and the lowest was associated with the right amygdala (0.2). Repeated measures anova revealed no site by session interaction. However, it revealed a main effect of session in the anterior cingulate cortex (session 1 lower values when compared to session 2). Moreover, around 70% of the regions had a site effect (UTSW had lower values when compared to the other two sites). Bilateral insula and amygdala and left ventrolateral cortex had no site effect.

Conclusions: Cerebral blood flow measured with arterial spin labeling revealed excellent/good reliability across sessions in both networks. Site had a variable impact on cerebral blood flow measure depending on the region of interest. The salience network was more stable across sites compared to the default mode network. Our excellent/good reliability measure paralleled other arterial spin labeling studies and highlights the importance of this non-invasive technique to investigate biomarkers in psychiatric populations using magnetic resonance imaging .

Keywords: arterial spin labeling, cerebral blood flow, controls, fMRI, reliability

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M73. Cortico-striatal GABAergic and Glutamatergic Dysregulations in Subjects at Ultra-high Risk for Psychosis Investigated with 1 H MRS

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Background: Dysregulations of the major inhibitory and excitatory amino neurotransmitter systems of γ-Aminobutyric acid (GABA) and glutamate have been described in patients with schizophrenia. However, it is unclear whether these abnormalities are present in subjects at ultra-high risk for psychosis (UHR). The aim of the present study was to measure levels of GABA and of the combined resonance of glutamate and glutamine (Glx) in the bilateral dorsal caudate and the medial prefrontal cortex of subjects at UHR and healthy controls.
Methods: Twenty-three antipsychotic naïve subjects at UHR and 24 healthy controls subjects, matched for age, sex, handedness, cigarette smoking, and parental education underwent proton magnetic resonance spectroscopy scans at 3 T. Levels of GABA and Glx were obtained using the standard J-editing technique and expressed as peak area ratios relative to the simultaneously acquired water signal.
Results: Significantly increased levels of GABA ($p<0.001$) and Glx ($p=0.007$) were found in the dorsal caudate of the subjects at UHR compared to the healthy controls. In the medial prefrontal cortex, likewise, both GABA ($p=0.03$) and Glx ($p=0.006$) levels were higher in the at UHR group than in the healthy controls. No group differences were found for any of the other metabolites (*N*-acetylaspartate, total choline or total creatine) in the two studied regions.
Conclusions: This study presents the first evidence of abnormal elevations, in subjects at UHR, of GABA and Glx in two brain regions that have been implicated in the pathophysiology of psychosis, warranting longitudinal studies to assess whether these neurotransmitter abnormalities can serve as noninvasive biomarkers of conversion risk to psychosis.
Keywords: GABA; Glutamate; 1 H MRS; Ultra-High Risk; Psychosis; Schizophrenia
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M74. Cortical Thickness as a Contributor to Abnormal Oscillations in Schizophrenia?

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Background: A core feature of neural ensembles is their oscillatory activity at various frequencies. Recent research, including work in our own laboratory, indicates that neural rhythms are distorted in schizophrenia, and that neural rhythms play a crucial role in sensory processing, symptom development and cognitive deficits. Although brain rhythms depend on brain structure (e.g., gray and white matter), to our knowledge associations between brain oscillations and structure have not been investigated in healthy controls (HC) or in individuals with schizophrenia (SZ). Observing function-structure relationships such as establishing an association between more 'normal' brain oscillations (defined in terms of amplitude or phase) and greater cortical gray matter, might inform treatment. The present study examined how superior temporal gyrus (STG) structure and age relate to auditory STG low-frequency and 40 Hz steady-state activity.
Methods: Thirty-nine individuals with SZ and 29 HC were recruited. 40 Hz amplitude-modulated tones of 1sec duration were presented. MEG and T1-weighted sMRI data were obtained. Using the single dipole sources localizing 40 Hz evoked steady-state activity (300 to 950ms), left and right STG total power and inter-trial coherence were computed. For analyses involving STG cortical thickness, in each hemisphere a composite score was calculated, with each STG subregion cortical thickness score (Hesch's Gyrus, Planum Temporale, Lateral Aspect) score scaled by its surface area. Time-frequency group differences and associations with STG structure and age were examined.
Results: Decreased total power and inter-trial coherence (ITC) in SZ were observed in the left STG for early low-frequency activity ($\sim$50 to 200ms, $\sim$4 to 16 Hz) as well as 40 Hz steady-state activity ($\sim$400 to 1000 ms). Left STG 40 Hz total power and inter-trial coherence were positively associated with left STG cortical thickness in HC, not in SZ. Left STG early low-frequency and 40 Hz total power were positively associated with age, again only in controls.
Conclusions: Present findings indicate profound disruption in STG auditory areas among SZ. Replicating earlier studies, analyses showed early STG low-frequency and 40 Hz steady-state total power and ITC abnormalities in SZ. STG function-structure relationships were observed only in HC, with STG gray-matter CT accounting for $\sim$13% of the variance in STG 40 Hz steady-state total power and $\sim$16% of the variance in 40 Hz steady-state ITC. In controls, associations with age were observed, with decreased left STG low-frequency and 40 Hz steady-state total power and ITC observed in older controls. Given the above function-structure and age-function abnormalities, present findings suggest that normalizing STG gamma oscillations in SZ may be difficult.
Keywords: schizophrenia, auditory, superior temporal gyrus, theta, alpha, gamma, magnetoencephalography

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M75. Lithium and Brain Glucose Metabolism in Patients with Bipolar-I Disorder

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Background: Although lithium is one of the most effective treatments for bipolar disorder (BD), 30–40% fail to respond. Furthermore, 10–20% of patients enjoy an excellent response to lithium with virtual elimination of symptoms. This wide inter-individual variation in response has been attributed to genetic differences in patients and this notion has been supported by family data. Together, these data have suggested the idea, that lithium responsive bipolar disorder is a mechanistically distinct form of illness. Considering 1–3% prevalence and 17% suicide rate in BD, there is a great clinical need to identify lithium responders in order to shorten the trial and error process of medication selection. However, no such predictor (either imaging or genetic) is available at this time. Our previous FDG-PET study in an earlier MSSM sample of bipolar-II (BD-II) patients showed decreased dorsolateral prefrontal and increased orbitofrontal and anterior cingulate uptake. Lithium administration was found to increase dorsolateral frontal and further increase in cingulate activity. In this present study we focused to determine if there is a specific pattern of brain activation associated with lithium response in BD- I patients. In line with the data and argument above, we hypothesized that lithium responsive BD is a mechanistically distinct subform of illness that will display specific pattern of regional brain activation and association to specific genetic variants.
Methods: To-date, our UCSD sample includes fifteen male healthy veteran volunteers (age = 29, SD = 7) and seven male BD-I subjects (age = 37,SD = 15) who underwent fluorodeoxyglucose, FDG-PET scanning 15 + 5-week after they were stabilized on lithium monotherapy (blood lithium 0.6- 0.9mMol/L). Neither age and nor CVLT differed significantly between groups. Subjects performed a modified California Verbal Learning Test (CVLT) during the 18-FDG uptake in a sound attenuated room. After 35 min of FDG uptake, they were moved to the Siemens EXACT HR + 961 PET tomography (CTI, Knoxville, TN) and underwent emission and transmission PET scans with attenuation correction. Images were normalized to the MNI brain, standardized by dividing by the whole brain mean, and AFNI-ROI applied. Statistical analysis t-Test maps were presented with a $p < 0.05$ threshold that compares BD-I subjects to control subjects. A region of interest (ROI) analysis was performed and other regions were tested as part of a secondary exploratory analysis using voxel based analysis with a $p < 0.01$ threshold.
Results: BD-I patients had significantly ($p = 0.03$, $t = 2.25$) higher relative glucose metabolic rates (0.96 SD = 0.04) than

the controls (0.91 SD = 0.05) in the subgenual cingulate, a result closely matching our earlier BD-II results on the effect of lithium. Significantly decreased relative glucose metabolic rate in the caudate ($p = 0.01$, $t = -2.61$), right medial dorsal nucleus ($p = 0.008$, $t = -2.98$) and the thalamus ($p = 0.01$, $t = -2.70$) and increased metabolic rates in the medial frontal gyrus ($p = 0.03$, $t = 2.23$) and nucleus accumbens ($p = 0.01$, $t = 2.74$) were observed.
Conclusions: Unlike antipsychotics or anxiolytics, lithium or valproate do not reduce brain glucose metabolism. Lithium treated BD-I patients show the same lithium changes previously observed in BD-II patients with orbitofrontal and medial-frontal cortex are being high and central gray structures (caudate thalamic nuceli) are being low in metabolic activity. Patients with high glucose metabolic rate in the anterior cingulate (Brodmann areas 25,24 and 23) and low glucose metabolic rate in the caudate and thalamic nuclei at the end of stabilization phase (pattern seen in our pilot data) will continue to respond to lithium. In progress accretion of non-responders will allow extension of this analysis to examine the functional neuroanatomy of lithium response. We are also conducting the regression analysis as minor allele count and an interaction term between activation and genotype.
Keywords: fluorodeoxyglucose cingulate gyrus prefrontal cortex thalamus
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M76. FDG-PET Scans in Patients with Good and Poor Prognosis Schizophrenia

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Background: Self-care and independent living are central features in poor prognosis schizophrenia. Cognitive deficits related to frontal dysfunctionidentified in brain imaging may be important. Frontal executive deficits are more prominent in neuropsychological test results from chronic patients than first episode patients and one might easily conclude that frontal executive skills are the most essential element in independent living. However, temporal lobe memory centers might be equally pivotal in daily life routines of medical appointments, drug compliance, shopping, and household maintenance.
Methods: We recruited 14 patients with poor outcome (Kraepelinian) schizophrenia (12 men and 2 women; mean age = 47 years old), according to Keefe's and colleagues criteria, 27 good outcome (non-Kraepelinian patients) (21 men and 6 women; mean age = 36.4 years old) and 56 age and sex matched healthy volunteers for comparison. We obtained FDG-positron emission tomography and coregistered scans to MRI for both voxel-by-voxel statistical mapping and stereotaxic regions of interest analysis.
Results: While both Kraepelinian and non-Kraeplinian patients showed equally lower uptake than healthy volunteers in the frontal lobe, the temporal lobes (Brodmann areas 20 and 21) showed significantly greater decreases in Kraepelinian than in non-Kraepelinian patients. Kraepelinian patients had lower FDG uptake in parietal regions 39 and 40, especially in the right hemisphere while non Kraepelinian patients had similar reductions on the left. Only Non-Kraepelinian patients had lower caudate FDG uptake than healthy volunteers. While both patient groups had lower uptake than healthy volunteers in the medial dorsal nucleus of the thalamus, Kraepelinian patients alone had higher uptake in the ventral nuclei of the thalamus. Kraepelinian patients also showed higher metabolic rates in white matter. We used classification tree analysis (CART, Salford Predictive Model Builder to further examine the good/poor outcome division. We selected five summary variables based the current findings and on previous research; dorsolateral prefrontal/occipital cortex and its associated relay point, the medial dorsal nucleus of the thalamus, the temporal lobe and its major thalamic nucleus, the pulvinar, and the caudate nucleus, the structure whose activity and volume are sensitive to antipsychotic effects. If Kraepelian and non-Kreplinian schizophrenia are two distinct types of schizophrenia, we would expect classification tree measures to identify a separation node between healthy and schizophrenia and then divide schizophrenia into Kraepelinian and non-Kraepelinian. Entry of this set of variables identified 70 of 96 subjects correctly (chi-square 55.5, df = 4, $p = 2.5 \times 10^{-11}$ and cross-validation using a leave-one-out analogue yielded 44/96 correct, 45.8%, chi-square 10.22, df = 4, $p = 0.036$. The first node was hypofrontality cut at > 0.76 which identified 45 of 55 healthy volunteers correctly and 24 of 41 patients with schizophrenia (see supplementary Figure 1). The pulvinar and whole temporal lobe volume further divide the subjects, 10/14 Kraepelinian subjects having hypofrontality, less active pulvinars, and less active temporal lobes. Models including the medial dorsal nucleus and cingulate divided healthy from patients with schizophrenia to a greater extent but the inclusion of these variables minimized the discrimination of Kraepelinian and non-Kraepelinian patients. The classification tree analysis thus supports a strong temporal lobe role in Kreapelinian schizophrenia.
Conclusions: Our examination of patients with either frontal and temporal lobe decreased vs. both decreased suggest that frontal or temporal function may to some extent compensate for deficits but that frontal and temporal inactivity together are especially disruptive to independent living.
Keywords: hierachical classification tree analysis, flurodeoxyglucose, prefrontal cortex, temporal cortex
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M77. Tau PET Imaging of Neurocognitive Disorders Using Newly Developed Tau Ligand [11C]PBB3

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Background: Senile plaques and deposition of intracellular tau fibrils are neuropathological hallmarks in Alzheimer's disease (AD). Tau pathology is considered to be closely related with neural dysfunction in AD and non-AD tauopathy, and could accordingly be an important target for both therapeutic intervention and diagnostic imaging. Here, we developed a novel positron emission tomographic (PET) ligands, phenyl/pyridinyl-butadienyl-benzothiazoles/benzothiazoliums (PBBs), for visualizing diverse tau inclusions in brains of living patients with AD or non-AD tauopathies and transgenic animal models of these disorders. In vivo optical and PET imaging of a transgenic mouse model demonstrated high affinity and selectivity for tau deposits by PBBs. Based on results from preclinical studies, a pyridinated PBB, [^{11}C]PBB3 was next applied in a clinical PET study. The aim of the present study was to investigate characteristics of [^{11}C]PBB3 in cognitively normal elderlies and patients with cognitive impairments.
Methods: Participants were 13 patients with AD, 6 patients with PIB-positive (amyloid positive) mild cognitive impairments (MCI) and 10 age-matched healthy controls (HCs). One patient with corticobasal syndrome (CBS) was also included as a preliminary examination. Their cognitive functions were assessed by Mini-Mental State Examination (MMSE). PET images were acquired by a Siemens ECAT EXACT HR + scanner. A dose (about 10 mCi) of [^{11}C]PBB3 was intravenously injected and sequential PET scans were performed for 70 min. Standardized uptake value ratio (SUVR) was calculated using the cerebellar cortex as reference region, and SUVR images were visually assessed in each subject. We also performed PET scan with a plaque-binding agent, [^{11}C]PIB (about 10 mCi), for 70 min and three-dimensional T1-weighted MRI. Cerebral plaque depositions were estimated using SUVR images at 50–70 min after [^{11}C]PIB injection. Parahippocampal grey matter volumes were estimated by voxel-based morphometry. Correlation analysis between MMSE score and mean cortical [^{11}C]PBB3 or [^{11}C]PIB bindings estimated by WFU pickatlas was performed among MCI and AD patients.
Results: All HCs and a patient with CBS were PIB-negative, and all MCI and AD patients were PIB-positive. SUVR images of [^{11}C]PBB3-PET demonstrated high accumulation of [^{11}C]PBB3 in the medial temporal cortex of all AD patients, in which binding of [^{11}C]PIB was minimal. Distribution of [^{11}C]PBB3 accumulation observed in AD patients extended to the entire limbic system and subsequently to the neocortex as a function of the disease severity. Interestingly, a subset of HCs also showed noticeable accumulation of [^{11}C]PBB3 confined to the medial temporal cortex, and exhibited mild parahippocampal atrophy. Significant correlation was shown between mean cortical [^{11}C]PBB3 binding and MMSE score among MCI and AD patients, whereas there was no significant correlation between [^{11}C]PIB and MMSE score. Furthermore, increased [^{11}C]PBB3 signals were found in a CBS patient negative for [^{11}C]PIB-PET.
Conclusions: The present study supported the utility of [^{11}C]PBB3-PET for detecting tau deposition *in vivo*, in light of distinct spatial distributions of [^{11}C]PBB3 and [^{11}C]PIB retentions in AD patients. Furthermore, the spread of [^{11}C]PBB3 binding may reflect the dementia severity, resembling progression of Braak tau stages. Moreover, the present study also provided the first evidence for in vivo detection of tau lesions in plaque-negative tauopathies. Our next stage clinical study with expanded sample size and wider range of MMSE scores including non-AD tauopatheis is currently ongoing. To understanding the significance of tau accumulation in various brain disease like traumatic brain injury, [^{11}C]PBB3 has potential to detect various types of tau accumulation in living human brain.
Keywords: Tau, PET, Alzheimer's disease, non-AD tauopathy, [11C]PBB3
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M78. Food Reward Circuitry Hyperactivation, Acylated Ghrelin, and Hedonic Capacity in Women with Remitted Major Depressive Disorder

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Background: Major depressive disorder (MDD) is characterized by abnormal responses to reward and stress. Stressful events can precipitate depressive episodes in individuals with a history of MDD, episodes which are further typified by changes in appetite and weight. These associations between weight outcomes and MDD symptoms (anhedonia, decreased/increased appetite) may be potentiated by abnormal activation in reward and limbic regions in response to food stimuli in individuals with MDD, given previous findings of hypoactivation in the hypothalamus, nucleus accumbens (NAcc), parahippocampal gyrus, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and insula during reward paradigms in MDD. Recent data by our group and others suggest a potential link between activation in these regions in response to rewarding food stimuli and peripheral acylated (active) ghrelin, a potent orexigenic peptide. Subregions of the hypothalamus, amygdala, and hippocampus demonstrate dense GHS-R1 receptor distribution, with further evidence from animal studies of the direct influence of ghrelin on mesoaccumbal reward circuitry. Ghrelin, therefore, may provide critical mechanistic insights into the associations between appetitive motivation and response to reward in MDD. In individuals with MDD, ghrelin levels have been found to be elevated, decreased, or similar to healthy controls, possibly due to differences in assay technique or other methodological variance. The aim of the current study was to examine the potential association between reward circuitry dysfunction, fasting acylated ghrelin levels, and food reward-related symptoms in women with remitted MDD.
Methods: Healthy-weight (BMI 20–24) female participants [11 women with recurrent Major Depressive Disorder, in remission (rMDD); 11 age- and BMI-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 3 T Siemens Trio MR scanner following a 14-hour fast. Fasting blood samples were drawn and acylated ghrelin levels were determined by radioimmonoassay. Participants completed the Eating and Appraisal Due to Emotions and Stress (EADES) and Snaith-Hamilton Pleasure Scale (SHAPS) to assess emotional/stress-related eating and hedonic capacity, respectively. Data analysis: fMRI data were analyzed using SPM8 to examine specific between-groups contrasts: High-calorie foods > objects; rMDD vs. HC. Regions of interest included: hypothalamus, NAcc, amygdala, hippocampus, insula, OFC, pregenual ACC (pgACC), and subgenual ACC (sgACC). Results from the single-subject level for these contrasts of interest were submitted to a second-level random effects regression analysis to examine the relationship between fasting acylated ghrelin and brain activity in response to high-calorie foods. For each group (rMDD, HC), acylated ghrelin levels entered as the covariate of interest, and specific relationships of interest (positive association, negative association) were tested using linear contrasts, and SPM maps were created based on these contrasts.
Results: Compared to HC women, rMDD women demonstrated *hyper*activation in response to high-calorie foods (vs. objects) in the hypothalamus [$t = 3.05$, p(FWE-corrected) = 0.05], amygdala ($t = 3.71$, $p = 0.03$), and sgACC ($t = 3.85$, $p = 0.004$) and hypoactivation in the hippocampus ($t = -3.89$, $p = 0.04$). rMDD women had marginally higher fasting acylated ghrelin levels to HC women ($t = 1.87$, $p = 0.07$). In the HC group, fasting ghrelin was positively associated with blood-oxygen-level-dependent (BOLD) activation to high-calorie foods > objects in the hypothalamus ($t = 4.67$, $p = 0.03$), amygdala ($t = 5.33$, $p = 0.04$), and hippocampus ($t = 4.66$, $p = 0.08$). In the rMDD group, there were no regions in which fasting ghrelin was positively associated with BOLD activation to high-calorie foods. However, rMDD women demonstrated a negative relationship between BOLD activation and fasting ghrelin in the hippocampus ($t = -3.88$, $p = 0.03$). Fasting ghrelin was also positively associated with emotional/stress-related eating in both HC ($r = 0.62$, $p = 0.04$) and rMDD ($r = 0.77$, $p = 0.01$) women, and with hedonic capacity in rMDD women ($r = 0.70$, $p = 0.02$), but not HC women ($r = 0.22$, $p = 0.52$).
Conclusions: In contrast to previous findings of reduced reward and limbic activation in response to positively-valenced stimuli in MDD, we report greater activation in the hypothalamus, amygdala, and sgACC while viewing high-calorie foods in women with rMDD compared to healthy controls, in addition to reduced activity in the hippocampus in rMDD. Furthermore, rMDD women demonstrated a positive relationship between ghrelin and both emotional eating and hedonic capacity but failed to display the typical association between fasting ghrelin and activity in homeostatic (hypothalamus) and hedonic (amygdala, sgACC) food motivation regions. These findings suggest dissociation between the ability to positively activate these regions and behavioral expression of feelings of stress-related eating and hedonic capacity. Overall, these results provide evidence that ghrelin may play a critical role in the pathophysiology of MDD and provide a framework for future studies to examine the pharmacogenetics of appetite dysregulation in MDD.

Keywords: Major depression, fMRI, appetite, ghrelin, reward
Disclosures: L. Holsen, Nothing to Disclose; K. Christensen, Nothing to Disclose; P. Moondra, Nothing to Disclose; A. Klibanski, Nothing to Disclose; J. Goldstein, Nothing to Disclose.

M79. Brain Injury in Battered Women and Its Relationship to Microstructural White Matter Alterations: A Diffusion Tensor Imaging Study

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Background: It is estimated that 25–50% of women will be abused by an intimate partner at least once in their lives, and 2–4 million are severely assaulted by partners each year. Women report a wide range of abusive acts that can cause traumatic brain injuries, in particular mild traumatic brain injuries (mTBIs) often resulting in the shearing and straining of axonal fibers, referred to as diffuse axonal injury (DAI). Although, brain injuries are considered a serious issue for battered women, virtually no empirical data exist on the prevalence of brain injury or its relationship to cognitive or psychological functioning. In an exception to this, our previous work demonstrated that nearly 75% of battered women sustained partner-related brain injuries, and 50% sustained multiple partner-related brain injuries, the severity of which was associated with partner-abuse severity, cognitive functioning, and psychopathology (Valera & Berenbaum, 2003). Building on these data, we used diffusion tensor imaging (DTI, an imaging technique sensitive to mTBI) to detect white matter abnormalities that possibly reflect DAI resulting from partner-related brain injuries.
Methods: Twenty-two women with a history of being in a physically abusive relationship underwent DTI imaging, as well as a semi-structured brain injury severity interview and completed a battery of cognitive and psychological assessment measures. Whole brain tractographic analysis was performed using FSL–DTI (FMRIB Oxford). Voxelwise assessment methods were applied to each woman's fractional anisotropy (FA) maps. FA values were compared between women with a limited number (range = 1–8) of mTBIs, Group 'BW1' (N = 11), and women with an extensive number (range = 20 +) of mTBIs, Group 'BW2' ($N = 11$). FA values were also correlated with number of mTBIs as well as scores from standardized tests of executive function, attention, memory and learning.
Results: DTI analysis demonstrated significantly decreased FA in the BW2 in comparison with the BW1 group in the splenium, right posterior corona radiata, right superior corona radiata and right corticospinal tract ($p = 0.05$; corrected for multiple comparisons). Direct neuroanatomical inspection identified the superior longitudinal fascicle II (SLF II) within these areas. FA of the splenium ($r = -0.57$, $p = 0.006$), right superior corona radiata ($r = -0.47$, $p = 0.030$) and right corticospinal tract ($r = -0.58$, $p = 0.004$) negatively correlated with the number of mTBIs. FA in the right superior corona radiata (including SLF II)

correlated positively with scores of memory and learning on the California Verbal Learning Test (r's = 0.48 and .45, p's = 0.022 and .037) and negatively with reaction time on a Continuous Performance Test ($r = -0.53$, $p = 0.011$).

Conclusions: To our knowledge this is the first neuroimaging study to examine brain injuries and show an association between partner-related mTBIs and measures of FA in battered women. More specifically, several white matter fiber tracts showed relatively reduced FA in the group of battered women who sustained an extensive number of brain injuries relative to women who sustained fewer brain injuries. Furthermore, FA in some of these regions was associated with performance on tasks of memory, learning and attention. The tracts showing reduced FA (the SLF II in particular) are generally associated with cognitive processes such as attention, working memory, spatial working memory and visuospatial attention. As such, the effects of these brain injuries could contribute to the attention and concentration difficulties many battered women report. Ongoing analyses of this dataset will continue to test these questions more directly. Nonetheless, these data suggest that more work is needed in this underserved and often disadvantaged population, as there are virtually no empirical data to date (in contrast to more high-profile sports-related brain injuries). These findings will hopefully contribute to battered women's health by helping women to better understand their situation as well as by effecting changes in legal and social policies pertaining to domestic violence. We also hope these data can serve to spur additional research examining the possible effects of intervention and treatment strategies directly following mTBIs (e.g., using beta-blockers as a protective factor).

Keywords: Battered women, mild traumatic brain injury, diffusion tensor imaging (DTI), diffuse axonal injury (DAI)

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M80. Examining Fronto-striatal Circuit Structure and Function in Treatment-naïve Children and Adolescents with Obsessive Compulsive Disorder

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Background: In obsessive compulsive disorder (OCD), altered fronto-striatal circuit structure is theorized to cause impaired circuit function, inhibitory control deficits and illness symptoms. Although neuroimaging studies indicate the presence of altered structure and function within fronto-striatal circuits in OCD, we have yet to understand how changes in structure relate to function to produce OCD symptoms. The examination of treatment-naïve children and adolescents with OCD provides a unique opportunity to learn about illness pathogenesis in the absence of confounding factors such as exposure to medication and chronic illness. In children and adolescents with OCD, neuroimaging studies have shown altered grey matter structure, excessive brain activity within fronto-striatal regions, and increased white matter integrity within frontal white matter tracts. In this pilot study, we used a novel multi-modal neuroimaging technique to examine how fronto-striatal circuit structure relates to function in treatment-naïve children with OCD, and whether this relationship differs to that seen in healthy controls. Diffusion tensor imaging (DTI) was used to examine white matter microstructure. Fronto-striatal circuit function was probed using a response inhibition (go/no-go) task and measured with magnetoencephalography (MEG).

Methods: Twelve treatment-naïve children with OCD (6 males, 6 females, mean age = 12 $\pm$ 1.9), and 12 healthy controls (7 males, 5 females, mean age = 12.6 $\pm$ 1.9) underwent MEG and DTI scanning. During MEG scanning, participants performed a visuo-motor go/no-go response inhibition task chosen to elicit fronto-striatal brain activation. The peak amplitude and latency for response-inhibition related frontal brain activation was recorded for each participant. Tract-based spatial statistics (TBSS) was then used to examine where MEG-derived measures of response-inhibition related frontal brain activity correlated with DTI-derived indices of white matter integrity (i.e., fractional anisotropy, FA) in treatment-naïve children with OCD and healthy controls.

Results: We did not find between-group differences in the relationship between response-inhibition related frontal brain activity and white matter microstructure using TBSS. However, in our within-subjects analysis of OCD participants, we found that the amplitude of response-inhibition related frontal brain activity correlated with FA within frontal white matter regions corresponding to the inferior fronto-occipital fasciculus, anterior thalamic radiations and cortico-spinal tract (multiple comparison corrected at $p < 0.05$). In contrast, no significant correlation was found between response-inhibition related brain activation and white matter microstructure across the brain in healthy controls. Follow-up analysis revealed that our findings were driven by the presence of a positive correlation between response-inhibition related frontal brain activity and frontal white matter microstructure in OCD, and the absence of this relationship in healthy controls.

Conclusions: Our pilot findings indicate that structure is tightly related to function within fronto-striatal circuits in treatment-naïve children and adolescents with OCD, a pattern that is not seen in age and sex-matched healthy controls. These findings may indicate that excessive activation of fronto-striatal circuitry in OCD leads to alterations in white matter microstructure or vice versa. In future we plan to examine whether altered fronto-striatal circuit properties relate to OCD symptoms and whether psychosocial and pharmacological interventions ameliorate these properties to bring about symptom improvement.

Keywords: Brain Circuits, Pediatric Obsessive Compulsive Disorder, Neuroimaging, Structure, Function

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M81. Multimodal Brain Connectivity Analysis using Functional-by-Structural Hierarchical Mapping

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Background: Many recent studies have separately investigated functional and structural connectivity, yet their relationship remains less understood. In this paper, we used functional-by-structural hierarchical mapping to integrate data from resting state fMRI (rsfMRI) data onto the whole brain tractography-derived structural connectome.
Methods: We describe functional-by-structural hierarchical (FSH) mapping as a novel technique that estimates the white matter structure underlying the resting-state functional connectivity, thus yielding the resting-state fMRI-informed structural connectome (rsSC). FSH assumes that the resting-state functional connectivity between two regions can be modeled as an exponential decay function of the 'modified' graph distance of the structural connectivity matrix subject to a white matter utilization matrix, which is estimated using simulated annealing. Using this technique, we investigated the rsSC from 7 depressed subjects and 7 age/gender matched controls. We examined the community structure of the rsSC using path length associated community estimation (PLACE).
Results: FSH mapping significantly improved the prediction of resting-state fMRI correlations, specifically for direct structural connections ($r = 0.287$, $p < 0.0001$ before mapping, $r = 0.472$, $p < 0.0001$ after mapping for healthy comparison subjects). Results revealed differential patterns of association in the bilateral posterior cingulate cortex and right precuneus, with the depressed group exhibiting stronger associations with regions instrumental in self-referential operations. Of note, no significant community structure differences were detected using connectomes derived from a single modality.
Conclusions: This preliminary study indicates the enhanced sensitivity obtained by integrating multimodal imaging data to understand group differences in brain connectivity. Using this novel technique, aberrant connectivity of medial structures involved in emotion and self-referential processing were detected.
Keywords: connectivity, fMRI, major depression, multimodal, neuroimaging
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M82. Modulation of Resting Brain Cerebral Blood Flow by the GABA B Agonist, Baclofen: A Longitudinal Perfusion fMRI Study in Marijuana Dependent Treatment Seeking Individuals

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Background: Preclinical studies confirm that the gamma-amino-butyric acid-B (GABA B) agonist, baclofen, blocks dopamine release in the reward-responsive ventral striatum (VS) and medial prefrontal cortex, and consequently, blocks drug motivated behavior. Clinically, baclofen, which is FDA-approved for other indications, has shown potential for reducing drug-motivated behaviors, including craving and relapse in opiate, cocaine, amphetamine, alcohol and most recently, marjiuana addictions. In nicotine-dependent smokers, we observed reductions in the number of cigarettes smoked per day in a *Baclofen for Smoking Reduction* clinical trial. Although it's mechanism of action has been clearly established in the animal literature, less work has been done in humans. Thus, work in our lab has focused on examining the effects of baclofen on neural and behavioral responses in several different drug-dependent populations. First, we demonstrated that baclofen reduced cocaine cue-induced craving, cocaine use, and brain activity (compared to nondrug cues) in the amygdala and medial orbitofrontal (mOFC) and anterior cingulate cortices. Next we demonstrated that both acute (20 mg) and chronic (3 weeks, 80 mg per day) baclofen reduced resting brain cerebral blood flow (CBF), in the nicotine-addicted brain in reward-related structures such as the VS, mOFC, amygdala and the anterior ventral insula. Studies are ongoing to determine if baclofen's modulatory effects on the resting brain predict responses to smoking cues. Here we sought to determine the effects of 3 weeks baclofen treatment on resting brain CBF in marijuana dependent treatment seekers. We hypothesized that baclofen treatment would reduce CBF in the brain at rest in the VS and its afferents including mOFC, amygdala and insula. Such knowledge might provide insight into its mechanism of action to reduce craving and decrease relapse rates in humans.
Methods: Twenty marijuana dependent subjects (12 males) were randomized to receive either baclofen (80 mg/day; $N = 9$) or placebo ($N = 7$). *Pseudo*-continuous arterial spin labeled (*p*CASL) perfusion fMRI was used to acquire five minutes of resting baseline data at two time points in 16 subjects; prior to randomization (Time 1) and approximately 3 weeks after randomization (Time 2). The 'quantitative' pCASL perfusion fMRI technique is ideal for longitudinal studies because it facilitates the measurement of medication-induced neural modifications. This technique is unique as these neural modifications are not observable using *relative* fMRI techniques, such as blood oxygen level dependent (BOLD) fMRI. SPM8 was employed to examine baclofen modulation of CBF across time (from Time 1 to Time 2) and across groups (baclofen versus placebo at Time 2).
Results: From Time 1 to Time 2, diminished CBF was observed in the mOFC, amygdala and ventral pallidum/striatum in baclofen-treated subjects, while no differences in CBF were observed in the placebo-treated group. At Time 2 CBF was diminished in the baclofen-treated subjects in the mOFC, ventral striatum and subgenual anterior cingulate cortex compared to placebo-treated subjects.
Conclusions: Here we extend our previous work in cigarette dependent individuals demonstrating baclofen modulation of the resting brain in a new population; marijuana dependent treatment seeking individuals. Studies are ongoing to determine baclofen's effects during marijuana cue

exposure and on treatment outcome. Baclofen's modulatory actions on regions involved in motivated behavior in humans are reflected in the resting state and provide insight into the underlying mechanism behind its potential to block drug-motivated behavior, in preclinical studies, and it's putative effectiveness as an anti-craving/anti-relapse agent in humans. Minimizing relapse rates and maximizing abstinence is crucial to the health of our nation and may be hastened by exploiting existing (and safe) medications, such as baclofen, that are potentially beneficial for drug addiction.

Keywords: baclofen, GABA B agonist, neuroimaging, marijuana dependence, ventral striatum, resting baseline perfusion fMRI, addiction

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M83. Chemokine-specific Relationships to AD Biomarkers in CSF in Healthy Older Adults

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Background: An upregulation of monocyte chemoattractant protein-1 (MCP-1) and other chemokines (Interleukin-8 [IL-8] and Interferon gamma-induced protein 10 [IP-10]) has been reported in MCI and mild Alzheimer's disease (AD). MCP-1 is one of the key chemokines that regulate migration and infiltration of monocytes/macrophages. In AD, higher CSF MCP-1, and IP-10 have been associated with higher MMSE scores, suggesting potential beneficial effects of chemokine upregulation. This may include possible effects on AD biomarkers (Abeta and tau indices), which are known to be implicated in preclinical AD. This study examined the relationship between CSF chemokine levels and established AD biomarkers in older individuals with Major Depressive Disorder (MDD), which is a risk factor for AD, and in healthy controls.

Methods: CSF was obtained from 47 older subjects with intact cognition and a Mini-Mental State Exam score of at least 28; 29 with MDD and 19 controls. MRI scans were performed to rule out structural brain abnormalities. No subject had gross MRI abnormalities other than white matter hyperintensities. CSF MCP-1, IP-10, IL-8, were determined using Luminex Corporation multiplexed bead-based immunoassays. Abeta40, Abeta42, total-tau, and p-tau were determined using previously published methods.

Results: MCP-1 was negatively correlated with CSF Abeta40 ($r = -0.376$, $p = 0.011$), total tau ($r = -0.361$, $p = 0.014$), and p-tau ($r = -0.361$, $p = 0.014$); IL-8 was positively correlated with t-tau ($r = 0.357$, $p = 0.015$); IP-10 was positively correlated with t-tau ($r = 0.380$, $p = 0.009$) and p-tau ($r = 0.323$, $p = 0.027$). None of the chemokines showed a significant correlation with Abeta42 or significant group differences.

Conclusions: Our findings suggest complex and differential associations between these chemokines and CSF AD Abeta and tau indices and highlight the need for further studies to determine their prognostic significance.

Keywords: Chemokine, MCP-1, IL-8, IP-10, Abeta

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M84. Varenicline Effects on Neural Reward Processing among Non-Treatment-Seeking Alcohol Dependent Individuals

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Background: The $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist varenicline has been reported to reduce drinking among both heavy-drinking smokers and primary alcoholics, and this effect may be related to varenicline-mediated reduction of alcohol craving. Among smokers, varenicline has been reported to modulate cigarette cue-elicited brain activation in several reward-related areas. The current study tested varenicline's effects on drinking and alcohol cue-elicited activation of reward-related brain areas among non-treatment-seeking alcohol-dependent individuals.

Methods: Thirty-five such individuals (mean age = 31, 57% male, 74% heavy drinking days in the past month, 15 smokers) were randomized to either varenicline (titrated to 2 mg) or placebo for 14 days, and were administered an alcohol cue reactivity fMRI task on day 14. *A priori* regions of interest (ROIs) were medial and lateral orbitofrontal cortex (OFC), right ventral striatum (VS), and medial prefrontal cortex (mPFC).

Results: Smokers drank less during the treatment period than non-smokers, but there was no main effect of medication or interaction between smoking and medication on drinking outcomes. Irrespective of medication, heavier smoking was associated with greater VS and right OFC activation, and the varenicline-treated group displayed less cue-elicited activation of bilateral OFC relative to placebo. Varenicline effects on VS activation were in the same direction but not significant ($p = 0.09$). However, there was no interaction between medication and smoking in any ROI.

Conclusions: These data partially support previous findings of varenicline effects on neural cue reactivity, and suggest that these effects are invariant to smoking status. Neuroimaging studies of individuals with more severe alcohol dependence are needed to further clarify varenicline's neurobiological mechanism of action in alcoholism.

Keywords: Nicotine, Chantix, fMRI, Neuroimaging, Craving

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M85. PACAP Receptor (ADCYAP1R1) Genotype Associates with Fear Responses in the Amygdala and Hippocampus in Highly-traumatized Civilians

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Background: We recently identified a single nucleotide polymorphism (SNP) in the gene coding for the PACAP receptor (*ADCYAP1R1*) that predicts PTSD in women and not men (Ressler, *et al*. 2011; Almli, *et al*. 2013). This SNP, rs2267735, is located on a canonical estrogen response element, indicating that estrogen levels may influence expression of the receptor. The *ADCYAP1R1* polymorphism has been shown to predict exaggerated arousal responses characteristic of PTSD in autonomic psychophysiology (Ressler *et al*. 2011; Jovanovic *et al*. 2012), but no study has yet examined the extent to which thispolymorphism influences fear-related responses in the human brain. The current study tests the hypothesis that *ADCYAP1R1* polymorphism influences the functional activity of brain regions that underlie emotional arousal, in particular, the amygdala and hippocampus, using MRI in a sample of women who have experienced civilian trauma. We also examined potential differences in amygdala connectivity between rs2267735 genotype groups.
Methods: Over 2000 male and female subjects were genotyped, and MRI data was obtained from 49 women ages 18–62 through an ongoing study of risk factors for PTSD. Salivary samples were collected to obtain DNA for genetic analysis, utilizing Taqman and Sequenom genotyping platforms, to define *ADCYAP1R1* risk genotype (CC) vs. non-risk (GC, GG) carriers. Self-reported psychiatric measures included the PTSD symptom scale (PSS), Traumatic Events Inventory (TEI), and the Childhood Trauma Questionnaire (CTQ). Genotyping of rs2267735 was conducted using Taqman and Sequenom platforms. The functional imaging task involved passive viewing of fearful and neutral face stimuli. This task has been shown to engage threat-processing networks in previous studies (Breiter, *et al*. 1996; Rauch, *et al*. 2000; Shin, *et al*. 2005), and the specific procedures are described elsewhere (Stevens, *et al*. 2013). Fearful and neutral face stimuli (Ekman and Friesen 1976) were presented in a block design. Trials included a face stimulus presented for 500 ms, followed by a 500 ms presentation of a fixation cross. Participants were instructed to pay attention to the faces.
Results: We found an *ADCYAP1R1* genotype by total trauma exposure interaction in females ($N = 858$, $p < 0.001$), but not males ($p > 0.1$). Moreover, this interaction was significant in females but not males after controlling for age ($p < 0.001$), income ($p < 0.01$), past substance abuse ($p < 0.001$), depression severity ($p = 0.02$), or child abuse ($p < 0.0005$), and all five covariates combined ($p = 0.01$). A meta-analysis with the previously reported samples revealed a strong association between PTSD symptom severity and an interaction between trauma and genotype in females ($N = 1424$, $p < 0.0001$). All fMRI analyses were performed using the contrast of fearful > neutral face stimuli. The *ADCYAP1R1* risk group showed significantly greater activation than the non-risk group in the amygdala ROI ($p_{corr} < .05$). When each group was examined separately, the risk group showed bilateral amygdala activation ($p_{corr} < .05$). The non-risk group did not show significant amygdala activation. In addition, the *ADCYAP1R1* risk group showed significantly greater activation than the non-risk group in the hippocampus ROI ($p_{corr} < .05$). When groups were examined separately, the risk group showed significant hippocampal activation bilaterally ($p_{corr} < .05$), whereas the non-risk group showed no significant cluster of activation. With functional connectivity analyses, we found that relative to the non-risk group, the risk group showed no region of enhanced connectivity with left or right amygdala. Instead, amygdala connectivity was significantly *decreased* in the risk group, relative to the non-risk group, for clusters in the left caudate, left and right lateral temporal cortex extending into superior parietal cortex, and right and left pre- and postcentral gyri.
Conclusions: We investigated individual differences in the functional activity of the amygdala and hippocampus associated with *ADCYAP1R*. Consistent with our hypotheses, individuals with the *ADCYAP1R1* risk genotype (CC) showed increased bilateral amygdala and hippocampal responses to fearful stimuli, relative to the non-risk group. Exaggerated neural responses to fearful stimuli are also characteristic of PTSD relative to traumatized control participants, particularly within the amygdala (Rauch, *et al*. 2000; Shin, *et al*. 2005; Stevens, *et al*. 2013). Individuals with the risk genotype also showed reduced functional connectivity between the amygdala and a network of cortical regions including medial prefrontal cortex (BA 10). Importantly, the risk group and non-risk group were matched for childhood abuse, lifetime trauma, PTSD symptoms, and depression symptoms. In sum, our studies suggest that variation in *ADCYAP1R1* impacts PTSD susceptibility in highly traumatized African American females, possibly via modulation/sensitization of amygdala and hippocampal responses.
Keywords: PTSD, PACAP, Genetic Amygdala, Hippocampus
Disclosures: K. Ressler, Nothing to Disclose; J. Stevens, Nothing to Disclose; L. Almli, Nothing to Disclose; N. Fani, Nothing to Disclose; D. Gutman, Nothing to Disclose; B. Bradley, Nothing to Disclose; S. Norrholm, Nothing to Disclose; E. Glover, Nothing to Disclose; T. Jovanovic, Nothing to Disclose.

M86. Association between Primary Insomnia and Major Depression: Distinct Entities or Spectrum Disorders?

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Background: Insomnia is one of the most common sleep disorders and has major individual and societal impact. Even though there is substantial comorbidity between major depression and insomnia, after accounting for sleep disturbances as a component of depressive episodes, there has been growing interest in studying primary insomnia that may cut across a range of other psychiatric and medical conditions. This presentation combines data from independent studies that have investigated the association between primary insomnia and major depression using a range of biologic measures including: (1) high density EEG (hdEEG) technology to look at brain activity in sleep in a clinical sample of patients; and (2) biomarkers of reactivity (e.g., startle response, heart rate reactivity (HRR)) and rhythms (activity, sleep, mood regulation) in a community based family study of the spectrum of mood disorders at the NIMH.
Methods: Samples: (1) Sleep: Patients with major depressive disorder, insomnia alone, and sex and age-matched controls ($n = 9$/group) from the University of Wisconsin Sleep Center; and (2) Startle/HRR: 186 people with primary insomnia, 154 with insomnia plus MDD, 257 with MDD alone and 283 controls without sleep problems from the community-based NIMH Family Study of Mood Spectrum Disorders. Measures and Methods: (1)Sleep: All-night sleep recordings with 256 channel hdEEG, including baseline waking recordings with auditory evoked potentials (AEPs) before and after sleep, were analyzed for non-depressed individuals with insomnia complaints, subjects with major depressive disorder and sex and age-matched controls without sleep complaints. Spectral analysis and cortical source localization (sLORETA) of the sleep data was conducted in order to examine both global and regional differences between groups. Statistical differences were assessed using analysis of variance, t-tests, and statistical non-parametric mapping, as a correction for multiple comparisons, where appropriate. (2)Startle/HRR: Anxiety-potentiated startle in response to predictable/unpredictable stimuli and heart rate reactivity were examined in probands with MDD, primary insomnia and their combination compared to controls.
Results: (1) Sleep: Beta and gamma activity were increased globally in both insomnia and depression relative to controls, but only alpha activity, particularly in deeper NREM (stage N3) sleep distinguished primary insomnia from depressed and control subjects. Increased alpha was greatest in somatosensory, auditory and visual cortices, as suggested by source modeling of alpha band activity. Both insomnia and depressed subjects failed to show sleep-related decreases in fast EEG activity and AEPs seen in normal control subjects when comparing waking prior to and following nocturnal sleep. Startle: There were statistically significant group differences in the magnitude of anxiety- potentiated startle, with those in Insomnia alone exhibiting the greatest reactivity ($X = 4.59$, s.d. $= 0.86$), compared to those with Insomnia + MDD ($X = 4.3$, s.d. $= 0.73$), MDD alone ($X = 3.14$, s.d. $= 0.6$) or controls ($XZ = 2.36$, s.d. $= 0.6$). HRR: Significant differences also emerged in the nightime very low power component with both insomnia groups (Insomnia alone: $X = 7.2$, s.d. $= 5.8$; Insomnia + MDD: $X = 7.14$, s.d. $= 0.2$) having significantly lower levels than those with MDD alone: ($X = 7.5$, s.d. $= 0.11$) or controls ($X = 7.6$, s.d. $= 0.09$).
Conclusions: Both insomniacs and depressives showed increased high frequency EEG during sleep and abnormal sleep homeostasis prior to and following nocturnal sleep. Only insomnia subjects, however, showed increases in alpha activity that were most prominent in primary sensory and associative cortices, suggesting that even during the deepest stage of sleep, sensory areas are still relatively active in insomnia comparison to control or depressed subjects. Likewise, biologic measures that were part of the endophenotype profile in the NIMH family study discriminated those with primary insomnia from those with major depression, suggesting at least partial independence of these syndromes suggesting greater reactivity of both startle and heart rate variability in those with insomnia. Taken together, these results suggest that although insomnia and depression are both characterized by significant abnormalities in sleep and other biomarkers, there are differences in specific aspects of their sleep and activity biomarkers that suggest their partial etiologic independence. Future studies of sleep, anxiety, reactivity, and related domains may facilitate our understanding of the common and unique biologic pathways underlying insomnia and depression.
Keywords: insomnia, depression, sleep, brain imaging, startle
Disclosures: R. Benca, **Part 1:** Merck, Sanofi-aventis; B. Riedner, **Part 1:** Philips Respironics, Also listed on several patents in process related to work with Philips Respironics, **Part 2:** 20% of salary paid by grant from Philips Respironics, **Part 3:** 20% of salary paid by grant from Philips Respironics, **Part 4:** 20% of salary paid by grant from Philips Respironics; M. Goldstein, Nothing to Disclose; L. Cui, Nothing to Disclose; A. Schmitz, Nothing to Disclose; J. Zhang, Nothing to Disclose; K. Merikangas, Nothing to Disclose.

M87. Neuroprotective Kynurenine Pathway Metabolites are Associated with Larger Hippocampal and Amygdalar Volumes in Patients with Major Depressive Disorder

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Background: Major Depressive Disorder (MDD) has been associated with reductions in hippocampal and amygdalar volume that are thought to reflect dendritic atrophy. MDD is also characterized by inflammation, shunting the metabolism of tryptophan away from the production of serotonin towards the synthesis of kynurenine (KYN) via the activation of the enzyme, indoleamine 2,3-dioxygenase (IDO). This process leads to the production of KYN metabolites, 3 of which are of principal interest: kynurenic acid (KA), a putatively neuroprotective *antagonist* of NMDA receptors, 3-hydroxykynurenine (3HK), a putative neurotoxin, and quinolinic acid (QA), an NMDA *agonist* that also exerts neurotoxic effects via lipid peroxidation, and disruption of the cytoskeleton and blood-brain barrier. Conceivably, the depression-related dendritic remodeling may be related to a pathogenic inflammatory process. Nevertheless, there are no extant data concerning the

relationship between peripheral molecular markers of inflammation such as the relative concentrations of kynurenine pathway metabolites and morphometric abnormalities in subjects with MDD.
Methods: Forty moderately-to-severely depressed unmedicated subjects who met DSM-IV criteria for MDD and 25 healthy controls (HCs) completed a structural T1-weighted whole brain MRI scan using an MPRAGE sequence optimized for tissue contrast (voxel volume $0.9 \times 0.9 \times 0.938\,mm^3$) and provided a blood sample for kynurenine metabolite analysis within 3 days of scanning. The kynurenine pathway metabolites were measured blind to diagnosis by Brains On-Line LLC using high performance liquid chromatography (HPLC). Hippocampal and amygdalar volumes were measured using the automated brain segmentation software, FreeSurfer. After excluding subjects who failed quality control checks of the metabolite analyses and FreeSurfer segmentations, 34 MDD subjects (age = 36.0 ± 9.9; BMI = 26.9 ± 4.6; 28 females) and 22 HCs (age = 35.7 ± 9.4; BMI = 28.8 ± 5.2; 13 females) had both valid MRI and metabolite data available for analysis. Since there were no significant diagnostic group differences in age, BMI and sex distributions, group differences in hippocampal and amygdalar volumes as well as kynurenine metabolites were measured by independent sample t-tests (2-tailed, $p < 0.05$). The Pearson correlation coeffient and/or linear regression (2-tailed, $p < 0.05$) were used to measure the relationship between the kynurenine pathway metabolites and the hippocampal and amygdalar volumes.
Results: The MDD group had nominally smaller whole brain grey matter (GM) volumes ($p > 0.1$), total hippocampal volumes ($p > 0.6$) and total amygdalar volumes ($p < 0.1$) than the HCs although these differences were not statistically significant. There were no significant group differences in the concentrations of KYN, KA, 3HK, and QA. However, the ratios of KA/3HK and KA/QA, putative neuroprotective indices, were lower in the MDD group relative to the HCs ($p < 0.05$). Because the MDD group had lower KA/3HK and KA/QA ratios than HCs and showed a trend towards smaller hippocampal and amygdalar volumes than HCs, analyzing the correlations between the kynurenine metabolites and the MRI measurements in the *entire* sample would by definition produce biased results. We therefore tested the correlation between the kynurenine pathway metabolites and the hippocampal and amygdalar volumes within the MDD group, only. Further, because sex was significantly correlated with KA concentration within the MDD group, we conducted this correlation analysis in the 28 depressed female subjects only. Within the female MDD group, age and BMI were significantly correlated with KA concentration. After regressing out the effect of age and BMI, the KA/QA ratio predicted total hippocampal volume (β-weight = 0.39, $t = 2.1$, $p < 0.05$) and total amygdala volume (β-weight = 0.39, $t = 2.2$, $p < 0.05$). In addition, the concentration of KA and the KA/3HK ratio showed a trend towards statistical significance for both total hippocampal and total amygdala volume (all p-values < 0.1).
Conclusions: The mian finding is that greater concentrations of neurotoxic to neuroprotective metabolites of kynurenine were associated with smaller hippocampal and amygdalar volumes in clinically depressed patients. This inflammation-GM volume relationship is consistent with preclinical reports and *in vitro* human studies which demonstrate inflammation-induced increases in kynurenine metabolism together with reductions in hippocampal neurogenesis and BDNF expression. These data raise the possibility that an inflammatory process contributes to the neuromorphometric abnormalities observed in some patients with MDD and conceivably adds to the evidence that abnormal NMDA receptor signaling may be the unifying mechanism underlying the glutamate and inflammation hypotheses of depression.
Keywords: Major depressive disorder; inflammation; MRI; kynurenine
Disclosures: J. Savitz, Nothing to Disclose; W. Drevets, **Part 5:** Janssen Pharmaceuticals of Johnson & Johnson, Inc.; T. Victor, Nothing to Disclose; J. Bodurka, Nothing to Disclose; K. Teague, Nothing to Disclose; R. Dantzer, Nothing to Disclose.

M88. Evaluating the Impact of Early Life Stress on DLPFC Functional Connectivity in Healthy Adults: Informing Future Studies of Transcranial Magnetic Stimulation

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Background: Early life stress (ELS) exposure is strongly associated with psychiatric disorders that prove resistant to treatment; one potential etiology of this phenomenon may be an inability for the brain to dynamically shift activity between internally focused networks, such as the default mode network (DMN), and networks that respond to external stimuli, such as the executive network. Previous studies have demonstrated that ELS is associated with decreased DMN resting state functional connectivity (rs-FC) as well as enhanced deactivations during executive tasks. This study evaluated whether ELS impacted rs-FC between executive and DMN networks, using the bilateral dorsolateral prefrontal cortex (DLPFC) as the principle seed for subsequent rs-FC calculations. We hypothesized that ELS exposure would be associated with greater dissociation between the DLPFC and the DMN, and that this disruption would be associated with ELS severity.
Methods: 27 medication-free healthy adult participants without psychiatric disorders (14 with ELS exposure) were scanned during 8 min of resting state acquisition using 3 T MRI. ELS was defined as at least moderate severity on the Childhood Trauma Questionnaire. Image preprocessing included the removal of images with greater than 1.5 mm movement to avoid the impact of motion on subsequent correlational analyses, in addition to standard preprocessing techniques. Rs-FC was evaluated by seeding the left and right DLPFC. DLPFC regions were anatomically defined for each participant by combining overlapping regions of bilateral Brodmann Areas 9 and 46, and expanding to a 25 mm cortical area. This original ROI was combined with an individual's segmented cortical ribbon at a probability of at least 75% to generate individually meaningful results. Rs-FC was compared between ELS and non-ELS groups, with whole-brain results corrected for family-wise error (FWE).

Results: Whole-brain rs-FC from the DLPFC revealed connectivity to expected executive network regions. When seeding the left DLPFC, ELS-exposed subjects demonstrated significantly increased rs-FC with the middle frontal gyrus (FWE-corrected $p < 0.001$) and decreased rs-FC with the left precuneus/posterior cingulate (FWE-corrected $p = 0.01$), compared to controls. When seeding the right DLPFC, ELS subjects demonstrated significantly decreased rs-FC with the contralateral precuneus/posterior cingulate (FWE-corrected $p < 0.001$) and inferior parietal lobule (FWE-corrected $p = 0.05$), compared to controls.
Conclusions: These findings highlight that ELS is associated with greater dissociation between the executive and default mode networks, with a prominent involvement of the left precuneus/posterior cingulate. These results have several implications. First it confirms that ELS, even in the absence of threshold psychiatric disorders, widely affects network level connectivity. Second, these results may have relevance to future studies of treatments using noninvasive brain stimulation. The seed region of this study, the DLPFC, is the principle target of repetitive transcranial magnetic stimulation (rTMS) treatment for major depression and posttraumatic stress disorder. As such, these results may inform neuroimaging assessments in future rTMS studies of ELS-related conditions.
Keywords: early life stress, functional connectivity, default mode network, dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation
Disclosures: N. Philip, Nothing to Disclose; T. Valentine, Nothing to Disclose; A. Tyrka, Nothing to Disclose; L. Price, Nothing to Disclose; L. Sweet, Nothing to Disclose; L. Carpenter, Nothing to Disclose.

M89. Persistent Cannabis Use During Adolescence Is Linked to Thinner Hippocampal Cortex in Late Life After Decades of Abstinence

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Background: Globally, marijuana (Cannabis sativa) is the most widely used illicit drug, with 18.1 million Americans reporting past month use in 2011 and 4.2 million meeting criteria for dependence *(U.S. Dept H&HS, Results from the 2011 National Survey on Drug Use and Health*). Understanding the biological implications of use is, therefore, critical to public health policy for this drug. Use during youth is especially concerning given the ongoing maturation in the adolescent brain, including the development of circuitry underlying memory performance and executive control (Jager, Block, *et al*, 2010 *J Am. Acad. of Child and Adolescent Psych*., **49;** Arseneault *et al*., 2002 BMJ, **325**). Because cannabis use appears to have a primary neurotoxic effect within the hippocampus (Chan, Hinds, 1998 *J. Neurol*., **18**), the main structure for memory and the structure affected most by age-related memory impairments and pre-clinical Alzheimer's disease (Braak and Braak, 1996, *Acta Neurol Scand Suppl*. **165**), we expect that the effects of chronic cannabis use may be substantial in senescence. A recent study reveals that cognitive deficits from chronic adolescent cannabis use persist into late-life, decades after the period of usage (Meier *et al*., 2012, PNAS, **40**). However, there is little information available regarding the long-term neurobiological effects of cannabis use, assessed in adults approaching late-life. This study investigated whether there are morphological differences late in life (average age = 60.3 years old) in subjects who used cannabis heavily in adolescence. We focused our investigation on the hippocampus, an area of the brain that is densely innervated with cannabinoid (CB)1 receptors (Burns *et al*., 2007, *PNAS*. **104**) and also is the primary site of age-related changes related to memory impairment and dementia. The dense concentration of CB1 receptors, which mediate the intoxicant effects of cannabis, suggests that any age-related changes that affect the hippocampus might interact with, and exacerbate, morphological differences resulting from chronic cannabis use.
Methods: We enrolled 28 subjects into two groups; 14 participants who used cannabis >14x/month for at least a year during adolescence ('Cannabis + ') and 15 participants who either did not use cannabis or used it less than once a week ('Cannabis–'). No participants were using cannabis at the time of assessment, as verified by urine test. Subjects provided self-reports of drug use. Cigarette smoking and alcohol use were allowed and matched across the two groups. In addition to light alcohol and tobacco use, groups were matched according to age, IQ, gender and mother's highest level of education. All subjects underwent high-resolution MRI through the long-axis of the hippocampus (3 T Allegra; TR: 5200ms, in-plane resolution: 0.4 mm x 0.4 mm, 3 mm thick skip 0) and neuropsychological testing. In order to increase visibility of the convoluted medial temporal lobe, the T2 FSE images were unfolded and flattened into a 2D map. Thickness values were calculated by taking the maximum of the distance values across all layers in the gray matter strip isolated within the MTL.
Results: Participants in the Cannabis + group had thinner cortex in late-life within the Cornu Ammonis 1,2,3 and the dentate gyrus, and thinner hippocampus averaged over all subregions. The magnitudes of these effects were significant in every region of the HC: 9.2% thinner CA23DG ($p = 0.005$), 20.8% thinner CA1 ($p = 3.8e\text{-}5$) and 22.4% thinner overall hippocampal thickness averaged across all subregions ($p = 7.8e\text{-}7$).
Conclusions: The results suggest that chronic use of cannabis in adolescence has long-lasting effects on hippocampal structure, which may underlie and exacerbate age-related cognitive decline. These findings are suggestive of a neurotoxic effect of cannabis use on the adolescent brain that persists well into adulthood, and they highlight the importance of public policy efforts that target adolescents.
Keywords: cannabis, MRI, hippocampus, thickness.
Disclosures: A. Burggren, Nothing to Disclose; B. Renner, Nothing to Disclose; E. London, Nothing to Disclose.

M90. Maternal Depression Affects Brain Responses to Baby Cry

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Background: Parenting constitutes a critically important, evolutionarily conserved set of attachment behaviors and associated thoughts elicited by infants to motivate maternal caring behaviors to soothe a distressed infant, provide instrumental and social care, and shape child development. Maternal behaviors are influenced by a mother's own life experiences and their working model of child, i.e., a suite of parenting-related thoughts. Upon perceiving a distress signal (baby cry), mothers respond to the children by activating their approach system, subserved by the reward neurocircuitry including midbrain, ventral striatum, anterior cingulate cortex (ACC), and prefrontal cortex (PFC), and deactivating their avoidance systems, subserved in part by the habenula. However, the capacity of mothers to generate caring behaviors may be compromised in mothers suffering from major depression disorder (MDD). Thus, in this functional magnetic resonance imaging (fMRI) study, we hypothesize that mothers with MDD will show brain responses associated with decreased positive motivations to care and increased fear, avoidance and helplessness-related responses to baby cry stimuli.
Methods: Thirty one mothers with MDD (n = 16) or not (n = 15) participated in the study, with a range of 2–7 years postpartum. In a Phillips 3 T scanner, the participants underwent a baby-cry task, in which mothers were instructed to listen to 30 second-blocks of random baby cries in 3 conditions and a control of pattern-matched white noise, preceded by one of three instructions: just listen to the baby cry ('Random-Baby-Cry'), imagine your baby crying ('Your-Baby-Cry'), or imagine that baby cries were of their own ('Self-As-Baby-Cry'). Data were analyzed with SPM 8.
Results: Across all 31 mothers, we found that, relative to white noise (Noise), listening to 'Random-Baby-Cry' differentially activated the approach and avoidance systems simultaneously, including the midbrain, striatum, amygdala, thalamus, insula, ACC, PFC, and habenula. For MDD vs. non-MDD controls, mothers showed reduced ventral striatum responses to 'Random-Baby' vs. Noise, indicating reduced approach/motivation/reward responses to baby cries in general, reduced ACC response to 'Your-Baby-Cry' vs. 'Random-Baby-Cry', indicating reduced attachment-dependent responses in the ACC, and greater habenula response to 'Self-As-Baby-Cry' vs. 'Random-Baby-Cry', potentially indicating elevated responses in brain circuits that subserve pain, stress, anxiety and learned-helplessness and inhibit motor responses.
Conclusions: Human parenting involves behaviors driven by key salient stimuli like baby-cries. This work makes use of neuroimaging tasks and the highly salient maternal stimuli of baby cries in order to explore maternal brain circuits that are altered by maternal depression. The results suggested that negative moods prevailing in depressed mothers attenuate the approach responses to baby cries in general, and thus decrease attachment response to one's own baby. Furthermore, depression is associated with brain response in regions relating to learned-helplessness. These preliminary brain-based explanations for decreased maternal sensitivity in postpartum depression may inform interventions to focus on perceived reward, efficacy and stress-response in mothers to reduce maternal depression and promote child development.

Keywords: brain, baby-cry, maternal, postpartum depression
Disclosures: J. Swain, Nothing to Disclose; S. Ho, Nothing to Disclose; K. Rosenblum, Nothing to Disclose; M. Muzik, Nothing to Disclose.

M91. Socially Rewarding Stimuli and Anhedonia Severity Among Depressed Adolescents

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Background: Anhedonia—the reduced capacity to experience pleasure—is a salient feature of major depressive disorder (MDD) and other psychiatric conditions. Among depressed adolescents, there is wide variability in anhedonia severity, often contributing to contrasting phenotypes. To date, limited research has accounted for this clinical phenomenology in reward-based investigations. Here, we sought to examine neural responses to social rewards in the context of anhedonia in adolescents. We focused on social rewards given that adolescence is a period characterized by heightened responsiveness to such rewards.
Methods: Subjects: Nineteen psychotropic medication-free adolescents with MDD and 18 healthy controls (HC), ages 12–20, were enrolled and assessed by a clinician using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (KSADS-PL). Depression severity was assessed using the clinician-rated Children's Depression Rating Scale-Revised (CDRS-R) and the self-rated Beck Depression Inventory (BDI). Anhedonia scores were computed by summing the responses to three anhedonia related items on the BDI (items 4: 'loss of pleasure' and 12: 'loss of interest') and CDRS-R (item 2: 'difficulty having fun'). MDD subjects met full DSM-IV-TR criteria, had episode durations $\geqslant$ 8 weeks, CDRS-R scores $\geqslant$ 39, and were psychotropic medication-free $\geqslant$ 3 months prior to the scan. HC did not meet criteria for any DSM-IV-TR diagnosis and were psychotropic medication-naïve. Face Task: All subjects were scanned during presentation of happy (i.e., social rewards), sad, fearful, and neutral faces and asked to judge either how sad the faces (i.e., emotional judgment) or how wide the noses (i.e., physical judgment) were on a scale from 1 (*very*) to 4 (*not at all*). Data Acquisition: A 3.0 T Siemens Allegra scanner was used to acquire functional T2*-weighted gradient echo images over 2 runs with 40 contiguous 3.0 mm axial interleaved slices with a 0 mm gap. High-resolution T1-weighted anatomical images were also acquired using a magnetization prepared gradient echo sequence. Preprocessing: Using AFNI, preprocessing included despiking, correction for slice-timing acquisition, and registration of images to a volume collected at the end of the functional scanning session. Analyses: Whole-brain group comparisons were carried out using AFNI's 3dttest + + while controlling for age and gender; Monte Carlo simulation was used to correct for multiple comparisons. In the MDD group, two voxel-wise regression analyses were carried out using 3dttest + +, with anhedonia scores

entered as the covariate of interest, along with age and gender. Lastly, two additional regressions were performed using depression severity, instead of anhedonia, as the covariate of interest.

Results: A comparison between the groups in response to happy faces revealed reduced activity in depressed adolescents in striatal and temporal regions. Within the MDD group, a right lateralized network of activity including dorsal prefrontal cortex, insula, and thalamus was uniquely associated with increased anhedonia severity for social rewards. Furthermore, we found greater activity in the precuneus and parietal regions in MDD adolescents compared to HC when viewing sad faces. A cluster in the dorsal anterior cingulate (DACC) was also uniquely associated with decreased anhedonia severity in the MDD group.

Conclusions: These findings suggest that in the context of social rewards, anhedonia may be related to processes underlying motivation, attention, and self-focus. Our work further highlights the importance of using both categorical and dimensional analyses in neurocognitive research in psychiatric disorders.

Keywords: fMRI, depression, adolescents, social reward

Disclosures: V. Gabbay, Nothing to Disclose; S. Henderson, Nothing to Disclose; A. Vallejo, Nothing to Disclose; R. Klein, Nothing to Disclose.

M92. Sleep Duration Contributes to Cortico-Limbic Functional Connectivity, Emotional Functioning, & Psychological Health

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Background: Insufficient sleep has numerous adverse effects on cognitive and emotional functioning. Previous research has shown that total sleep deprivation is associated with degradation of some aspects of emotional intelligence, constructive thinking, frustration tolerance, and moral judgment, as well as increased severity on indices of psychological disturbance. While the causes of these changes are poorly understood, neuroimaging evidence suggests that sleep deprivation is associated with decreased metabolic activity in the prefrontal cortex and reduced prefrontal-amygdala functional connectivity. These alterations have been hypothesized to contribute to impaired top-down modulation of emotion. While such findings are apparent during prolonged total sleep deprivation, it remains unknown whether this altered connectivity may be observed during more typical levels of sleep curtailment, such as that experienced by most individuals from time to time. We examined whether self-reported sleep duration the night before the assessment would be associated with these effects.

Methods: Sixty-five healthy adults (33 men, 32 women), ranging in age from 18–45 years documented their hours of sleep from the night preceding the assessment session, completed the Bar-On Emotional Quotient Inventory (EQ-i), Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), Personality Assessment Inventory (PAI), and underwent a 6-min eyes-open resting-state functional magnetic resonance imaging (fMRI) on a 3 T scanner. Connectivity data were analyzed using the Functional Connectivity Toolbox for SPM8. Correlations between functional connectivity and self-report inventories were Bonferroni corrected at $p < 0.05$.

Results: Greater self-reported sleep the night preceding the assessment was associated with higher scores on all scales of the EQ-i but not the MSCEIT, and with lower symptom severity scores on half of the psychopathology scales of the PAI, including reduced Anxiety, Depression, Paranoia, Schizophrenia, Alcohol Related Problems, and greater Treatment Resistance. Likewise, longer sleep duration was also associated with stronger inverse functional connectivity between the right ventromedial prefrontal cortex and right amygdala. These connectivity values were extracted and correlated with emotion and psychopathology scores. Overall, greater inverse connectivity between these regions was associated with higher EQ-i and lower symptom severity on the PAI, including Anxiety, Anxiety Related Disorders, Depression, Paranoia, Schizophrenia, Borderline Features, Suicide, and Stress, and greater Treatment Resistance.

Conclusions: Self-reported sleep duration from the preceding night was significantly correlated with inverse prefrontal-amygdala connectivity, perceived emotional intelligence, and the severity of subjective psychological distress. These data suggest that even small variations in sleep of only 1 or 2 h—a variation in sleep duration that is frequently encountered in everyday life—may be significantly associated with differences in some aspects of perceived emotional intelligence and the severity of psychological distress. Conversely, getting a full night of sleep appears to be connected with bolstered emotional strength and mental health.

Keywords: sleep; functional connectivity; emotional intelligence; anxiety; depression

Disclosures: W. Killgore, Nothing to Disclose.

M93. A Longitudinal MR Spectroscopy Study of the Anterior Cingulate Cortex and Hippocampus Before and After Antipsychotic Treatment in Patients with Schizophrenia

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Background: Understanding the mechanisms underlying drug response in patients with schizophrenia is an important step in identifying biomarkers of treatment response. Recent cross-sectional and longitudinal studies suggest antipsychotic medications may modulate glutamate and *N*-acetylaspartate (NAA). In addition, few studies have focused on the effects of antipsychotic medications on choline. In this study, we used proton MR spectroscopy to test the hypothesis that treatment with the antipsychotic risperidone alters glutamate + glutamine (Glx), NAA, and choline in the dorsal anterior cingulate cortex (ACC) and hippocampus of patients with schizophrenia. Specifically, based on prior work, we hypothesized that Glx in the hippocampus would decrease with treatment and that the

abnormal relationship between Glx and NAA would be restored in the ACC but not the hippocampus following treatment. We further hypothesized that levels of choline would decrease with treatment.

Methods: 20 patients with schizophrenia and 20 matched healthy controls were included in this study. Patients were scanned at baseline (off medication), and after 1 week and 6 weeks of treatment with risperidone. All imaging was performed on a 3 T Siemens Allegra. MRS voxels were prescribed the bilateral dorsal ACC ($2.7 \times 2.0 \times 1.0$ cm) and the left hippocampus ($2.7 \times 1.5 \times 1.0$ cm). Manual shimming was performed, and CHESS pulses were used to suppress the water signal. Water-suppressed spectra were collected with the point-resolved spectroscopy sequence [PRESS; TR/TE = 2000/80 msec, 1200 Hz spectral bandwidth, 1024 points, ACC: 256 averages, hippocampus: 640 averages]. MRS spectra were processed in jMRUI. The residual water peak was removed using HLSVD filter. Spectra were quantified in the time domain by the AMARES algorithm. Prior knowledge for Glx was obtained by scanning a phantom solution of 20 mmol/L glutamate in buffer (90 mmol/L Na^+, pH 7.1, 37° C) and quantifying the resulting spectrum in jMRUI. The AMARES model consisted of peaks for NAA, choline (Cho), creatine (Cr), and three peaks for glutamate and glutamine (Glx). Paired-samples *t*-tests were used to compare metabolite levels. Pearson's correlation coefficients were used to assess the relationship between metabolites and treatment response, defined as the improvement in total score on the Brief Psychiatric Rating Scale (BPRS). Statistical significance for all tests was $p < 0.05$.

Results: There was a significant reduction in patients' symptoms (BPRS) from baseline to week 1 [paired $t(19) = 4.37$, $p < 0.001$] and from baseline to week 6 [paired $t(19) = 7.98$, $p < 0.001$]. Paired-samples one-tailed *t*-tests comparing baseline and week 6 MRS levels in the hippocampus revealed a trend-level reduction in Glx/Cr [paired $t(19) = 1.54$, $p = 0.07$], a significant increase in NAA/Cr [paired $t(19) = 1.88$, $p = 0.04$], and a significant reduction in Glx/NAA [paired $t(19) = 1.99$, $p = 0.03$]. In both the ACC and hippocampus, Cho/Cr increased from baseline to week 1 and then decreased at week 6. Paired-samples two-tailed *t*-tests showed a significant decrease in Cho/Cr in the ACC from week 1 to week 6 [paired $t(19) = 2.415$, $p = 0.03$] and a significant increase in the hippocampus from baseline to week 1 [paired $t(19) = 2.626$, $p = 0.02$]. In the ACC, there was no significant correlation between Glx/Cr and NAA/Cr at baseline [$r(18) = 0.28$, $p = 0.24$]. However, Glx/Cr and NAA/Cr in the ACC were significantly correlated following 1 week of treatment [$r(18) = 0.69$, $p = 0.001$] and 6 weeks of treatment [$r(18) = 0.55$, $p = 0.01$]. In the hippocampus, Glx/Cr and NAA/Cr were not correlated before or after treatment [baseline: $r(18) = -0.21$, $p = 0.39$; week 1: $r(18) = 0.33$, $p = 0.16$; week 6: $r(18) = -0.24$, $p = 0.31$]. The improvement in the BPRS total score after 6 weeks of treatment was positively correlated with the baseline off-medication Glx/Cr level in the ACC [$r(18) = 0.48$, $p = 0.03$].

Conclusions: In the dorsal ACC, the correlation between Glx and NAA usually observed in healthy controls was restored with treatment, and unmedicated Glx levels were correlated with treatment response. In the hippocampus, there was a significant reduction in Glx/NAA over the course of treatment, but the Glx-NAA correlation was absent regardless of medication status. In both the ACC and hippocampus, patients demonstrated the same pattern of choline increase and decrease across treatment, possibly indicating a short-term increased membrane breakdown/turnover or an inflammatory response. Our findings suggest that regionally specific glutamate abnormalities are present in unmedicated patients with schizophrenia and that antipsychotics appear to modulate glutamate function in a manner that is regionally specific. Therefore, ACC Glx may become a useful predictor of treatment response to antipsychotic medications and the disrupted hippocampal Glx-NAA correlation an important trait marker of the illness that could guide the development and testing of new drugs. A focus on choline in future longitudinal studies will be of great benefit to the field, both in understanding the underlying pathology of schizophrenia as well as mechanisms of drug response.

Keywords: schizophrenia, spectroscopy, glutamate, NAA, treatment response

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M94. Glutamate Levels Determined with Magnetic Resonance Spectroscopy (MRS) in the Medial Prefrontal Cortex of Patients with Psychosis as Compared to Healthy Volunteers

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Background: Abnormalities in glutamatergic transmission are believed to be an important contributor to the pathophysiology of schizophrenia, however evidence supporting this is mostly indirect, especially in vivo. Measures of glutamate levels in schizophrenia have been obtained in vivo with proton MRS, however the majority of this literature is based on methods that do not allow separation of glutamate from glutamine and GABA. A recent meta-analysis indicated that while glutamate levels in the prefrontal cortex were generally reduced in patients with schizophrenia as compared to healthy volunteers, this effect was much more prominent with advancing age. Here, we provide data from 27 patients with psychosis and 47 controls of similar sex and age (ranging between 18 and 53). The MRS acquisition allowed for detection of glutamate alone.

Methods: 47 healthy volunteers (26.7 ± 6.1 SD years old, 22 females) and 27 patients with schizophrenia (27.9 ± 8.1 years old, 8 females) participated in this study. MRS was collected in the medial prefrontal cortex (MPFC) on a GE 3 T scanner with a TE-averaged sequence (Hurd *et al.* 2004: 32 different echo times, 4 averages per echo, TE was started at 35 ms, and increased by 6 ms for each of the 31 following echoes). Reference unsuppressed water scans were collected

immediately after spectral data acquisition, enabling determination of water T2. Raw data were saved and processed with programs developed in-house (Zhang, Shen 2013). Institutional units of glutamate referenced to the water signal (GLU) and ratios of glutamate/creatine (Glu/Cre) were analyzed as dependent variables. Backward stepwise regression models were used with age and sex as covariates for analysis of Glu/Cre, and age, sex and cerebrospinal fluid (CSF) content for analysis of GLU. All 2-way interactions were initially included in the model and main effects were forced into the model.

Results: There were no significant differences in age or sex distribution between the two diagnostic groups (unpaired t-test). The patients with schizophrenia had significantly increased CSF content in the acquired voxel (7.6% ± 6 SD for controls vs. 11.1% +/-7 in patients, $p = 0.03$), but no significant difference in the composition of gray and white matter between groups. There was a trend for the T2 of water to be decreased in patients with schizophrenia (70.6 +/-1.7 in controls vs. 69.7 +/-2 in patients, $p = 0.07$), and a significant increase of the Cramer-Rao Lower Bounds (CRLB, a measure of quality control) for GLU (5.6 +/-0.75 in controls vs. 6 +/-1 in patients). The overall regression models were significant for both Glu/Cre (multiple $R^2 = 0.28$, $F_{3,70} = 9.24$, $p = 0.000032$) and GLU (multiple $R^2 = 0.24$, $F_{4,69} = 5.4$, $p = 0.00078$). For Glu/Cre, there was a significant effect of diagnosis ($F_{1,70} = 12.7$, $p = 0.00068$), with patients having lower glutamate levels than controls, and a significant effect of age with Glu/Cre decreasing over the age span ($F_{1,70} = 12.2$, $p = 0.00082$), but no interaction of age by diagnosis (ns). For GLU, there was a significant effect of diagnosis ($F_{1,69} = 6.3$, $p = 0.014$), and a significant effect of age with GLU decreasing over the age span ($F_{1,69} = 7.2$, $p = 0.009$) but no significant interaction of age by diagnosis. No other interaction was significant. These results remained statistically significant when water T2, and GLU CRLBs were used as covariates in the multiple regression models.

Conclusions: These data confirm a reduction of glutamate levels in the medial prefrontal cortex of patients with schizophrenia as compared to normal controls, and a reduction of glutamate levels with age, however there was no increased rate of glutamate reduction with age in patients with schizophrenia as compared to controls in this cohort. Further research is needed to address the effects of illness duration, illness severity and neuroleptic treatment on glutamate levels. The main limitation of this study is that the patients were all chronically treated with neuroleptics. Another limitation is the somewhat reduced quality of glutamate fitting in patients, although when this was accounted for statistically, the group effect remained significant. Because tissue GLU levels do not distinguish between mobile aminoacid and neurotransmitter pools, they cannot address the underlying neurotransmission changes.

Keywords: glutamate, MRS, schizophrenia, aging

Disclosures: S. Marenco, Nothing to Disclose; Y. Zhang, Nothing to Disclose; A. Slagle, Nothing to Disclose; S. Kuo, Nothing to Disclose; C. Meyer, Nothing to Disclose; A. Sethi, Nothing to Disclose; A. Barnett, Nothing to Disclose; J. Shen, Nothing to Disclose; D. Weinberger, Nothing to Disclose; K. Berman, Nothing to Disclose.

M95. Longitudinal Effects of Antipsychotic Treatment on Functional Connectivity of the Striatum in Patients with First-episode Psychosis

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Background: Previous evidence has implicated corticostriatal abnormalities in the pathophysiology of psychosis. All known antipsychotic agents that show efficacy against psychotic symptoms target D2 receptors, which are most abundant in striatal regions. The implications of treatment with antipsychotics and subsequent reduction in positive symptoms on brain function and circuits of the striatum remain largely unknown. In recent years resting state fMRI has become a useful tool for investigating functional connectivity without the influence of task-based activation. Additionally, first episode patients with psychosis are a unique population with minimal prior exposure to antipsychotic medications. The present study examined the longitudinal effects of treatment with second generation antipsychotics on functional connectivity of the striatum during the resting state in patients experiencing a first-episode of psychosis.

Methods: Twenty-four patients experiencing their first-episode of psychosis, and twenty-four healthy controls, matched for age, sex, and handedness participated in the study. Patients were scanned during the resting state and evaluated with the Brief Psychiatric Rating Scale (BPRS) at baseline and following twelve weeks of treatment with either risperidone or aripiprazole. Healthy volunteers were scanned during rest at baseline and 12 weeks later, but were not treated. BOLD fMRI was collected and functional connectivity of dorsal and ventral striatum were examined with a seed-based approach using 6 regions of interest (ROIs) within the striatum in each hemisphere as per a previous study. For each ROI, the baseline scan was subtracted from the follow-up scan (follow-up - baseline) using fslmaths. This image representing the change in correlation between the ROI and all other voxels was then taken into a group level multiple regression analysis with reduction in positive symptoms (baseline - follow-up) as a regressor. This analysis was performed separately for each ROI, explicitly masked within a binary mask from the corresponding control network. Significance was determined at $p < 0.05$, corrected for FDR.

Results: Antipsychotic treatment resulted in a significant reduction in positive symptoms ($T = 7.35$, $p < 0.0001$), which was measured by combining items reflective of psychosis from the BPRS. Our healthy control group showed no significant changes in functional connectivity in analyses of all 12 of our seed ROIs when baseline scans were compared with follow-up scans. Our patients showed a robust area of increased connectivity between the right dorsal caudate and prefrontal regions, including the anterior cingulate and the dorsolateral prefrontal cortex as symptoms improved. The left inferior ventral striatum showed a significant increase in connectivity as positive symptoms decreased in the left hippocampus. The right

ventral rostral putamen showed increased connectivity with anterior cingulate and right anterior insula, similarly as symptoms improved.
Conclusions: Consistent with previous evidence, our results further support the role of corticostriatal links in psychosis. Our findings indicate that improvement in symptoms with the treatment of second generation antipsychotics results in increased functional connectivity between the striatum and the prefrontal cortex, as well as limbic regions.
Keywords: first episode psychosis, resting state, fMRI, second generation antipsychotics, striatum
Disclosures: D. Sarpal, Nothing to Disclose; D. Robinson, **Part 1:** Consultant: Shire, Asubio, 3D Communications , **Part 4:** Bristol Myers Squibb; Janssen; T. Lencz, Nothing to Disclose; T. Ikuta, Nothing to Disclose; M. Argyelan, Nothing to Disclose; K. Karlsgodt, Nothing to Disclose; J. Gallego, Nothing to Disclose; J. Kane, **Part 1:** Alkermes , Amgen, Bristol-Meyers Squibb , Eli Lilly , Forrest, Genentech, H. Lundbeck A/S , Intracellular Therapeutics , Janssen Pharmaceutica , Medavante, Merck , Novartis , Otsuka Pharmaceutical , Reviva , Roche, Sunovion , Pierre-Fabre, **Part 2:** Bristol-Meyers Squibb, Otsuka Pharmaceutical , **Part 4:** Genentech – pending; P. Szeszko, Nothing to Disclose; A. Malhotra, Nothing to Disclose.

M96. Multimodal Analysis of Brain Networks Structural and Functional Connectivity Changes in Non-medicated Late-life Depression

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Background: As a common psychiatric disorder in growing geriatric population, Late-life depression (LLD) has a negative impact on the cognitive, affective and somatic function of older adults. The aim of this study is to analyze the resting-state functional connectivity and white matter microstructural alterations in a group of geriatric unmedicated patients with LLD ($n = 10$) compared to a healthy control group ($n = 15$).
Methods: A whole-brain ROI-wise approach was used for measuring functional connectivity changes and an automated tract-based spatial statistics (TBSS) method was applied for quantifying white matter tract integrity alteration in terms of fractional anisotropy (FA).
Results: Our results showed a decrease in connectivity between the right accumbens area and the right medial orbitofrontal cortex and between the right rostral anterior cingulate cortex and bilateral superior frontal gyrus in depressed subjects. We also detected a 20% decrease in FA in the right Forceps Minor (rFM) fasciculus in depressed group. Significant correlations were found between functional connectivity values and symptoms severity. Furthermore, values of FA showed a significant correlation with values of FC in total sample and depressed group.
Conclusions: Our results suggest that dysfunction in the networks mediating cognitive control and reward processing play an important role in the pathophysiology of LLD.
Keywords: Late-life depression, Functional Connectivity, Structural Connectivity, Resting-state fMRI, TBSS
Disclosures: R. Tadayon-Nejad, Nothing to Disclose; S. Yang, Nothing to Disclose; A. Kumar, Nothing to Disclose; O. Ajilore, Nothing to Disclose.

M97. Neural Response During Indirect and Direct Processing of Emotional Faces Predicts Improvement Following Cognitive Behavioral Therapy in Generalized Social Anxiety Disorder

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Background: Generalized social anxiety disorder ('gSAD') is characterized by exaggerated fears of potential scrutiny and heightened neural sensitivity to threat-relevant signals as evidenced by exaggerated amygdala and/or insula activity and aberrant anterior cingulate cortex (ACC) activity during direct and indirect threat perception. Cognitive Behavioral Therapy (CBT) is an evidence-based psychotherapy for gSAD, which is associated with reduced threat processing bias in those who respond to treatment. Little is known about whether aberrant brain responses to direct and indirect threatpredict CBT success in gSAD.
Methods: Twenty-one patients underwent functional magnetic resonance imaging (fMRI), in a task involving viewing images comprising a trio of faces (angry, fear, or happy) alongside a trio of geometric shapes (circles, rectangles, or triangles) within the same field of view and either matching faces or matching shapes, effectively directing attention towards or away from emotional information, respectively. All participants then completed 12 weeks of individual CBT. Pre-treatment task-related brain activation data were entered into a whole-brain analysis of covariance, regressing pre-CBT to post-CBT change in the Liebowitz Social Anxiety Scale 'LSAS' (while controlling for initial severity) to index clinical improvement.
Results: Brain predictors of clinical improvement following CBT were localized to the dorsal ACC, medial prefrontal cortex (mPFC), rostral ACC, and amygdala, but not the insula. Specifically, greater pre-CBT activation of dorsal ACC and mPFC while attending to faces predicted greater LSAS symptom reduction. In contrast, less pre-CBT activation of rostral ACC and amygdala when attending away from faces predicted greaterLSAS symptom reduction. Post-hoc regression analysis to examine the specificity of emotional valence of faces on these brain-improvement associations showed that fear faces significantly contributed to the dorsal ACC finding whereas faces across expressions (angry/fear, and happy) contributed to mPFC, amygdala, and rACC results.
Conclusions: Findings indicate individuals with enhanced pre-CBT activity in dorsal prefrontal regions when attending to emotional faces and/or less activity in amygdala and rostral ACC when attending away emotional faces are more likely to benefit from CBT possibly due to an attention-mediated emotion regulation ability that is capitalized on by CBT. Activity was not limited to threat faces, which suggests heightened sensitivity to social-emotional cues regardless of valence are relevant to CBT response. Furthermore, the lack of insula results indicates certain regions implicated in the

pathophysiology of gSAD may not serve as predictors of treatment success. Future work is needed to determine if the brain predictors observed here are specific to CBT or shared across any evidence-based therapeutic modality (e.g., pharmacotherapy) and/or across other internalizing psychopathologies for which CBT is a standard treatment.
Keywords: social anxiety disorder; brain imaging; fMRI; emotion processing, psychotherapy
Disclosures: H. Klumpp, Nothing to Disclose; D. Fitzgerald, Nothing to Disclose; D. Post, Nothing to Disclose; K. Phan, Nothing to Disclose.

M98. The Effect of Electroconvulsive Therapy on Emotional Processing in Major Depressive Disorder: A Neuroimaging Study

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Background: Electroconvulsive therapy (ECT) is the most effective treatment in pharmacologically resistant depression, however, its mechanism of action is still unknown. Previous neuroimaging studies with FDG and rCBF PET implicate frontal lobe changes during ECT treatment, but have failed to show a direct relationship with the most reliably replicated area in neuroimaging studies of major depressive disorder, the subgenual cingulate region. This study examined the potential effects of ECT treatment in patients with major depressive disorders utilizing a paradigm of activation of brain regions involved in emotional processing.
Methods: Eleven depressed patients (age: 47.4 ± 11.8) undergoing bifrontal ECT treatment and nine healthy controls (age: 45.6 ± 12.0) participated in a longitudinal neuroimaging study, imaging involving three timepoints. Before undergoing any ECT treatment, each patient underwent a baseline fMRI session (T1) while being shown images of positive, negative, or neutral emotional value in 30 s blocks. These images were previously assigned valence and arousal values by the International Affective Picture System in order to filter for nonspecific brain activations and to balance the arousal levels between different emotional domains. An identical second session (T2) was completed within 36 h of the patient's first ECT, and the third and final session (T3) within 36 h of the last ECT, but no later than the 8^{th} ECT. Healthy individuals underwent the same imaging protocol, but no ECT was applied. The fMRI scans were processed using the FSL FMRI Expert Analysis Tool (FEAT) to compare levels of brain activation across trials and between subject groups. We contrasted blocks with images of positive and negative value against those with images of neutral value (valence). Patients were assessed prior to each ECT treatment with the Hamilton Rating Scale for Depression (HRSD-24), using a remission criterion of attaining scores
Results: 8 out of 11 patients achieved remission on ECT treatment (baseline HAMD 28 ± 7, HAMD at 3rd fMRI: 13 ± 8, paired t test $p < 0.01$). Heightened activity in the subgenual cingulate was detected in depressed patients during the first baseline session ($p < 0.001$, uncorrected), while the healthy controls had much higher levels of activation throughout widespread cortical regions of the brain, including the inferior lateral occipital cortex (Brodman's area 19), the anterior cingulate (area 32), the cerebellum, the pons and the midbrain. Interestingly, activity in the subgenual cingulate decreased for depressed patients after the first ECT (both T1 versus T2 and T1 versus T3 contrasts, $p < 0.001$, uncorrected), while activity increased in the dorsolateral-prefrontal region only at the end of the course of ECT treatment (T1 versus T3 and T2 versus T3 contrasts, $p < 0.001$, uncorrected). Post-hoc analysis in the subgenual cingulate (mask was created based on baseline contrast between healthy controls and patients) revealed that these changes represent normalization of activation (post hoc $p < 0.05$), similar to the activity in the fMRI sessions of healthy controls. Further analysis, however, could not detect a correlation between baseline clinical symptoms/response and the activation level/change in subgenual cingulate. In contrast, baseline DLPFC activation correlated significantly with the change in HRSD-24 scores ($p = 0.02$, $R^2 = 0.77$). Patients whose baseline DLPFC was more activated by emotionally charged images had greater clinical response to bifrontal ECT.
Conclusions: The presence of an active subgenual cingulate in T1 depressed patients, coupled with the similarities between ECT-treated depressed patients and healthy controls, suggests that ECT can successfully alter the neural networks associated with depression. These results further support the idea that the subgenual cingulate region plays a pivotal role in the pathophysiology of depression, though they indicate that it is not the sole determinant of clinical outcome. The identification of the additional neural substrates that presumably interact with this important area is the next logical step for future studies. Our results suggest that baseline DLPFC could be such a neural component and could serve as a potential biomarker in the treatment of depression. Indeed, our baseline comparison showed that DLPFC was underactivated in depressed patients, implying that the more 'normal' the DLPFC the higher the chance for a favorable response. Future studies will investigate the clinical role of interactions between the DLPFC and subgenual cingulate.
Keywords: ECT, Major Depressive Disorder, fmri, emotional processing, subgenual cingulate
Disclosures: M. Argyelan, Nothing to Disclose; S. Kaliora, Nothing to Disclose; H. Hanna, Nothing to Disclose; T. Ikuta, Nothing to Disclose; P. Kingsley, Nothing to Disclose; D. Sarpal, Nothing to Disclose; P. Szeszko, Nothing to Disclose; A. Malhotra, Nothing to Disclose; G. Petrides, Nothing to Disclose.

M99. Categories and Dimensions of Anxiety and Depression in the Resting fMRI Signal

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Background: A challenge to improving psychiatric nosology is to determine relative contributions of dimensional and categorical variables to psychopathology. A rich potential

source of information for linking neurobiology to these variables is the resting state fMRI signal. Given a common genetic diathesis for generalized anxiety disorder (GAD) and major depressive disorder (MDD) as well as a shared higher order anxious misery factor common to anxiety and depression, a neurobiological assessment of shared and distinct variability according to GAD/MDD diagnosis as well as dimensions of anxiety and depression is sensible.
Methods: Resting fMRI data were collected from 90 medication-free participants (38 healthy controls, 17 GAD only, 12 MDD only, and 23 comorbid GAD/MDD) in a cross-sectional study. *A priori* regions of interest analysis focused on the amygdala, subgenual cingulate cortex, ventral striatum, hippocampus, dorsolateral and medial prefrontal cortices, fronto-insular cortex, and dorsal and subgenual anterior cingulate cortex according to low frequency signal amplitudes and functional connectivity. Parallel analysis data reduction followed by principle component regression were used to test separately categorical (GAD or MDD vs. non), dimensional (MASQ anxious arousal, anhedonia, general distress), and mixed (categorical and dimensional) models of neurobiological fluctuation.
Results: We found support for both overlaps between anxiety and depression, as well as condition-specific abnormalities. Specifically, an MDD diagnosis and the broad symptom dimension of general distress together best explained low frequency resting-state signal amplitudes, primarily in limbic/paralimbic regions (amygdala, hippocampus, ventral striatum, subgenual cingulate). The dimension of general distress overlapped considerably variability otherwise attributable to GAD, but the symptom dimension of anhedonia did not substantially overlap variability explained by an MDD diagnosis. No consistent anxiety or depression results were established according to functional connectivity using categorical or dimensional measures.
Conclusions: These data suggest that use of a single conceptual framework alone (i.e. categorical diagnoses or symptom dimensions) may provide an incomplete mapping of psychopathology to neurobiology, at least with respect to resting-state fMRI data. Use of a broad neurobiological measure, as is possible through resting-state fMRI, has thus provided a powerful brain-based test of dominant conceptual models of anxiety and depression developed through the study of symptoms and comorbidities.
Keywords: neuroimaging, nosology, neurobiology
Disclosures: D. Oathes, Nothing to Disclose; A. Schatzberg, **Part 1:** PharmaNeuroBoost, BrainCells, CeNeRx, Cervel, Lilly, Corcept, Merck, Xhale, Somaxon, Takeda, Jazz, PSK, Forest Labs, Delpor MSF, **Part 3:** PharmaNeuroBoost; A. Etkin, Nothing to Disclose.

M100. Changes in Cortical Thickness in Children of Parents with Bipolar Disorder

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Background: Children of parents diagnosed with Bipolar Disorder are at higher risk to develop mood disorders (High-Risk offspring). Functional imaging studies have commonly implicated abnormal functioning of the emotional processing networks in this population. Many of such studies implicate the anterior cingulate, dorsolateral and ventrolateral prefrontal regions and suggest that these abnormalities preceded the onset of any disorder (Ladouceur *et al*, 2013). Structural imaging studies have reported increased gray matter volume in the right inferior frontal gyrus and hippocampal/parahippocampal regions in relatives of individuals with Bipolar Disorder (Hajek *et al*, 2013). Cortical structure can also be examined using cortical thickness, which can give greater insight into spatial location of regional irregularities. In this study, we used a cortical thickness analysis to compare surface-based morphometry of high-risk offspring and age-matched healthy controls.
Methods: High resolution Magnetic Resonance images were collected of 40 individuals using a 3.0 Tesla Scanner. Of these, 12 were healthy children of healthy parents (HC: average age = 13.20 ± 2.7 years, 8 females, average IQ = 116.17 ± 12.5) and 28 were 'high risk' with at least one parent diagnosed with bipolar disorder (HR: average age = 13.39 ± 2.9 years, 13 females, average IQ = 110.57 ± 17.5). The high risk group included both symptomatic and asymptomatic children. The presence or absence of symptoms in the high-risk offspring was confirmed using the K-SAD-LP interview. Cortical thickness was analyzed using the program Freesurfer (http://surfer.nmr.mgh.harvard.edu/). Cortical thickness was defined using the distance between pial surface to the gray/white matter border at each vertex. Surface maps were smoothed with a 10 mm full-width-half-maximum Gaussian kernel. Comparison of the two groups was done using ANCOVA with sex, age and IQ as covariates. Values have not been corrected for multiple comparisons due to small sample size ($p < 0.001$ uncorr). Moreover, we performed an analysis comparing the correlations between cortical thickness and either anxiety (Multidimensional Anxiety Scale for Children (MASC)) or depression (Child Depression Inventory (CDI)) scores.
Results: The HR group demonstrated thinner cortex in the left superior parietal ($t = 3.55$) right inferior temporal ($t = 3.92$), and the right superior temporal sulcus ($t = 3.20$). The HR group also showed thicker cortex in the right caudal/anterior cingulate ($t = -3.72$). Furthermore, comparing the interaction of cortical thickness and MASC scores ($N = 40$), we found opposite relationships in the right inferior parietal ($t = -3.44$), right lateral occipital ($t = -3.36$) and a trend in the left precuneus ($t = -3.08$). In all three cases, the MASC-cortical thickness correlation was negative in the HC group and positive in the HR group. Similarly, we found a difference in the right superior parietal ($t = -3.40$, $N = 40$) for the interaction between cortical thickness and CDI scores between the two groups. Once again the HR group CDI-cortical thickness correlation was positive while the HC group correlation was negative.
Conclusions: These results suggest cortical thickness changes in offspring of parents with bipolar disorder compared to children of healthy parents. As brain function is related to structure, these results may help to further understanding of underlying psychopathology associated with risk of being the offspring of a parent with bipolar disorder.

Keywords: Neuroimaging, offspring, bipolar disorder, cortical thickness
Disclosures: R. Sassi, **Part 1:** Speaker and consulting honorarium from Bristol Myer Squibbs and Jansen Pharmaceutics. ; L. Hanford, Nothing to Disclose; L. Minuzzi, Nothing to Disclose; G. Hall, Nothing to Disclose.

M101. Myelin and Axon Abnormalities in Schizophrenia and Bipolar Disorder Measured with Magnetization Transfer Ratio and Diffusion Tensor Spectroscopy

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Background: Diffusion tensor imaging has provided evidence for white matter abnormalities in both schizophrenia (SZ) and bipolar disorder (BP). However, diffusion tensor imaging measures, which are commonly interpreted as indices of 'white matter integrity,' are relatively non-specific, and do not differentiate between axon- and myelin-specific abnormalities. Here, we combine magnetization transfer ratio (MTR) and diffusion tensor spectroscopy (DTS) to measure indices of myelin sheath thickness and axon geometry separately in SZ and BP. MTR measures magnetization exchange of protons between 'free' water molecules and water molecules that are 'bound' to myelin lipids. The more myelin is present, the more proton exchange occurs, and the higher is the MTR. DTS measures the diffusion of intracellular metabolites, such as N-acetylaspartate (NAA). Because NAA is located exclusively in neurons and almost exclusively in the cytosol where diffusion is less restricted than within organelles, NAA diffusion provides specific information about intra-neuronal structure. In a previously published study (F. Du *et al*, *Biological Psychiatry* 2013), we used the combined MTR-DTS approach to probe white matter abnormalities in SZ, and found significantly reduced MTR (suggesting reduced myelin content) and significantly elevated apparent diffusion coefficient of N-AA (suggesting abnormal intra-neuronal content) in SZ patients compared to age- and sex-matched healthy control participants. Here, we extend our study of microstructural white matter abnormalities to include patients with psychotic BP.
Methods: Following approval by the McLean Hospital Institutional Review Board, we studied 23 patients with SZ, 7 patients with psychotic BP, and 22 age- and sex-matched healthy control participants. Data from the SZ patients and healthy control participants were previously published; data from the psychotic BP patients were newly acquired, with data collection in this group ongoing. MTR: we used a BISTRO saturation pulse train constructed with multiple hyperbolic Sec pulses (width 50 msec) with varied radiofrequency pulse amplitudes and applied at the beginning of a standard point-resolved spectroscopy (PRESS) sequence (before the 90-degree pulse) to saturate 'bound-water' signal with a specific frequency offset. Data were obtained in 50-Hz steps at a range of frequencies offset 400–1000 Hz in either direction from the water signal, and a single MTR number was calculated by averaging across frequencies. Saturation time (t_{sat}) was 2.6 sec with repetition time/echo time of 3000/30 msec and 2 repetitions. We collected data from a $1 \times 3 \times 3$ cm voxel within the right prefrontal cortex white matter at 4 Tesla. DTS: The standard PRESS sequence was modified by incorporating diffusion gradients for DTS measurements. Bipolar diffusion gradients with six directions and one control (totaling seven spectra) were applied to calculate diffusion tensors of signal from water and metabolites. The applied b value was 1412 sec/mm^2. Repetition time/echo time was 3000/135 msec, and diffusion time (D_t) was 60 msec. There were 96 repetitions for metabolites and 4 repetitions for water measurements. Metabolite spectra were acquired with water saturation with VAPOR.
Results: MTR was significantly reduced in both SZ (mean $0.15 \pm$ SD 0.03) and psychotic BP (0.15 ± 0.01) compared to healthy control participants (0.17 ± 0.02). The apparent diffusion coefficient of N-acetylaspartate (NAA-ADC) was significantly elevated in SZ (0.25 ± 0.05), compared to healthy control participants (0.21 ± 0.05). Patients with psychotic BP had NAA-ADC (0.23 ± 0.04) intermediate between SZ and healthy control participants. We calculated the NAA-ADC to MTR ratio as an index of axon to myelin geometry; this ratio was 1.66 ± 0.39 in SZ, 1.53 ± 0.26 in psychotic BP, and 1.35 ± 0.27 in healthy control participants.
Conclusions: The results suggest that white matter abnormalities in SZ and psychotic BP include both abnormal myelination and abnormal NAA diffusion within axons. The NAA-ADC to MTR ratio, reflecting the relationship between axonal geometry and myelin thickness, is highest in SZ, followed by psychotic BP, then healthy control participants. The degree of demyelination appears to be similar in SZ and BP. The index of axonal geometry, on the other hand, is largest in SZ and intermediate between SZ and healthy control participants in psychotic BP. These results suggest that abnormalities in signal transduction and information processing lie on a continuum, with white matter disease among these three groups most severe in SZ, and intermediate between SZ and healthy control participants in psychotic BP. It remains unclear whether differences in these processes, particularly axonal geometry, are associated with the disease process or possible compensatory mechanisms.
Keywords: Schizophrenia, Bipolar Disorder, Magnetization Transfer Ratio, Diffusion Tensor Spectroscopy, White Matter
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M102. Brain White Matter Development Is Associated with a Human-specific Haplotype Increasing the Synthesis of Long Chain Fatty Acids

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Background: The genetic and molecular pathways driving human brain white matter (WM) development are only beginning to be discovered. Long chain polyunsaturated fatty acids (LC-PUFAs) have been implicated in myelination in animal models and humans. The biosynthesis of LC-PUFAs is regulated by the fatty acid desaturase (FADS) genes, of which a human-specific haplotype is strongly associated with LC-PUFA concentrations in blood. To investigate the relationship between LC-PUFA synthesis and human brain WM development, we examined whether this FADS haplotype is associated with age-related WM differences across the lifespan in healthy individuals aged 9–86 years.
Methods: Diffusion tensor imaging was performed to measure fractional anisotropy (FA), a putative measure of myelination, of major brain WM tracts. FADS haplotype status was determined with a single nucleotide polymorphism (rs174583) that tags this haplotype.
Results: Overall, normal age-related WM differences were observed, including higher FA values in early adulthood compared to childhood, followed by lower FA values across older age ranges. However, individuals homozygous for the minor allele (associated with lower LC-PUFA concentrations) did not display these normal age-related WM differences (significant age-by-genotype interaction $p = 0.000$).
Conclusions: These findings suggest that LC-PUFAs are involved in human brain WM development from childhood to adulthood. This haplotype may play a role in human neurodevelopmental disorders in which both compromised LC-PUFA metabolism and myelination have been implicated, such as schizophrenia.
Keywords: white matter, myelin, diffusion tensor imaging, brain development, fatty acid desaturase genes.
Disclosures: B. Peters, Nothing to Disclose; A. Voineskos, Nothing to Disclose; P. Szeszko, Nothing to Disclose; T. Lett, Nothing to Disclose; P. DeRosse, Nothing to Disclose; S. Guha, Nothing to Disclose; T. Ikuta, Nothing to Disclose; D. Felsky, Nothing to Disclose; M. John, Nothing to Disclose; J. Kennedy, Nothing to Disclose; A. Malhotra, Nothing to Disclose.

M103. Ketamine Reduces Left Nucleus Accumbens Volume within 24 H of Treatment of Major Depressive Disorder Patients

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Background: Preclinical models of depression have shown dendritic shrinkage, reduced spine density, and a decrease in BDNF functioning in the hippocampus and medial prefrontal cortex of stressed animals. These pathophysiological changes are believed to underlie the hippocampal and cortical volumetric reductions observed in patients with Major Depressive Disorder (MDD). In contrast, stress has been associated with increased BDNF, spine density, and overall synaptic strength in the nucleus accumbens (NAc) of animals. In this study, we investigated whether these preclinical findings of enhanced neuronal remodeling in the NAc would translate into an increase in NAc volume in MDD subjects. We then studied the association between NAc volume and history of treatment resistance as well as the effect of ketamine, a rapid-acting antidepressant, on the NAc volume.
Methods: Thirty-three medication-free MDD (14 treatment-resistant (TRD) & 19 non-TRD) and 26 healthy controls received high-resolution magnetic resonance imaging (MRI) to estimate left and right NAc volumes using the Freesurfer fully automated processing recon-all pipeline. A separate sample of 16 TRD who had failed to respond to at least 3 antidepressant medications received a single infusion of subanesthetic dose of ketamine (0.5 mg/kg infused over 40 min) under double-blind conditions. Patients underwent structural MRI the day before infusion and 24 h post-treatment. A linear mixed model was constructed using all available pre/post-ketamine successful MRIs to examine the effect of ketamine on NAc volume. Age showed a significant effect on NAc volume and thus was included as covariate in all analyses.
Results: Controlling for intracranial volume, we found larger left NAc in MDD subjects compared to healthy controls (Mean ± SEM: MDD = $605 \pm 18\ mm^3$, Healthy = $488 \pm 20\ mm^3$, $F_{(1,56)} = 18.5$, $p < 0.001$). The comparison of TRD, non-TRD, and healthy groups showed a significant group effect ($F_{(2,55)} = 9.3$, $p < 0.001$). Post-hoc comparison with Bonferroni correction revealed larger left NAc in non-TRD ($p = 0.001$) and TRD subjects ($p = 0.01$), compared to healthy. Left NAc volume did not differ between TRD and non-TRD ($p > 0.1$). No statistically significant differences were observed in the right NAc. Pre-/post-ketamine comparison showed a modest but statistically significant reduction in left NAc volume (Mean difference ± SEM = $-33 \pm 15\ mm^3$, $F_{(1,25)} = 5.0$, $p = 0.05$).
Conclusions: Consistent with preclinical data, we found for the first time enlarged left NAc in patients with MDD. Interestingly, ketamine has been previously shown in rodents to reverse the effect of chronic unpredictable stress on spine density and synaptic strength within 24 h of administration. In parallel, in our small sample of TRD patients, ketamine induced a modest reduction in left NAc volume within 24 h of treatment, an intriguing finding that warrants further investigation in future definitive studies.
Keywords: ketamine, MDD, antidepressant, nucleus accumbens, MRI.
Disclosures: C. Abdallah, Nothing to Disclose; A. Jackowski, Nothing to Disclose; R. Salas, Nothing to Disclose; S. Gupta, Nothing to Disclose; J. Sato, Nothing to Disclose; L. Chang, Nothing to Disclose; X. Mao, Nothing to Disclose; J. Coplan, **Part 1:** JDC is on the Pfizer advisory board and gives talks for BMS, AstraZeneca, GSK, and Pfizer, **Part 4:** JDC received grant support from NIMH, NYSTEM, GlaxoSmithKline, Pfizer, and Alexza Pharmaceuticals.; D. Shungu, Nothing to Disclose; S. Mathew, **Part 1:** Dr. Mathew received consulting fees from AstraZeneca, Naurex, Roche, and Takeda. Dr. Mathew has been named as an inventor on a pending use-patent of ketamine for depression. Dr. Mathew has relinquished his claim to any royalties and will not benefit financially if ketamine is approved for this use., **Part 4:** Supported by NIMH grant R01 MH-081870, NARSAD Independent Investigator Award, The Brown Foundation,

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M104. Visual Hallucinations in Patients with Schizophrenia Are Associated with Visual Cortex Hyperconnectivity to Amygdala and Hippocampus

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Background: While auditory verbal hallucinations (AH) are a common symptom of schizophrenia, visual hallucinations (VH) also occur in about 50% of patients who endorse AH. Visual hallucinations are generally under-appreciated by neuroscientists interested in schizophrenia, perhaps because they are more likely to occur in neurological disorders. Symptom capture studies of AH in schizophrenia patients reveal involvement of speech production and speech reception areas, as well as areas of the brain involved in emotion experience and memory. Symptom capture studies of VH in neurological patients reveal ventral extra-striate activity even in the *absence* of hallucinations. Functional connectivity analyses of fMRI data have exploited the temporal correlation of activity from an *a priori* 'seed' region with activity in other brain regions. Functional connectivity may reflect a type of functional scaffolding that is set up between different areas of the brain, when they are repeatedly co-active, recalling the old adage 'cells that fire together, wire together.' That is, functional connectivity does not necessarily reflect current activity, but may reflect the ability for these areas to communicate efficiently with each other and support conscious experience. By taking advantage of a large sample of patients and controls studied as part of the 7-site FBIRN consortium (Function Biomedical Informatics Research Network), we were able to compare patients who endorsed both auditory and visual hallucinations (AHVH) to those endorsing only AH.
Methods: We collected resting state fMRI data from 178 patients with schizophrenia and 180 age- and gender-matched healthy controls (HC). Patients were grouped according to SAPS ratings on auditory hallucinations (AH) and visual hallucinations (VH). We compared patients with both AH and VH (AHVH; $n=42$), patients with AH but no VH (AH; $n=50$), patients with neither AH nor VH (noH; $n=67$), and HC. Patients given a 'questionable' rating on AH or VH were excluded ($n=21$). Of note, only 2 of the 178 patients endorsed VH in the absence of AH. We did a seed-based connectivity analysis using left amygdala (because of its role in fear and negative emotion), bilateral hippocampus (because of its role in memory), and bilateral parahippocampal gyrus (because of its role in threat and uncertainty) as anatomically-defined, non-over-lapping seeds. The 4 groups did not differ in age, sex, or handedness. Other than having more severe visual hallucinations, AH and AHVH groups did not differ on SAPS measures. To account for possible site differences, connectivity values for patients were first z-scored against HC values for each of the 7 sites. Second, we compared z-score connectivity maps from AH to AHVH patients. Third, significant clusters ($p<0.05$, FWE corrected) from the AH vs. AHVH comparison formed masks for the extraction of connectivity values from each group (clusters of interest, COI). Fourth, using two-sample t-tests, we compared the AHVH and AH groups to the noH and HC groups for each COI.
Results: AHVH patients had greater connectivity between left amygdala and both left and right visual cortex than AH patients, noH patients and HC. The visual cortical COIs were dominated by voxels in higher order visual areas (BA18/19, fusiform and lingual gyrus), involved in feature extraction, face processing, and attribution of intentions. Bilateral hippocampus connectivity showed a similar pattern, with AHVH patients having greater connectivity than the other groups. Similarly, AHVH patients had greater connectivity between bilateral parahippocampal gyrus and putamen, insula, and temporal pole than the other groups. The AH patients showed less connectivity with amygdala, reflecting anti-correlations with visual cortex, perhaps supporting suppression of visual representations of voices. Generally, AHVH, HC and noH groups showed positive connectivity between seeds and clusters.
Conclusions: Patients with schizophrenia who endorse visual hallucinations have hyperconnectivity between cortical areas subserving higher order visual processing and subcortical areas subserving memory and emotion. This hyperconnectivity is unique to this group of patients and is not seen in patients who endorse AH in the absence of VH, in schizophrenia patients who endorse neither, or in healthy controls. This functional scaffolding allows associations between faces, memories, and emotions.
Keywords: Visual hallucinations, functional connectivity, amygdala, hippocampus, visual cortex, schizophrenia
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M105. Baclofen Reduces Resting Blood Flow, and Correlations with Limbic Cue Reactivity, in the Ventral Striatum of Cocaine-dependent Men

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Background: Baclofen is a GABA B receptor agonist that has shown promise for the treatment of cocaine dependence. Baclofen attenuates the self-administration of cocaine in animal models of addiction and has been reported to blunt cocaine craving and/or reduce use in cocaine-dependent individuals. While preclinical studies indicate that baclofen

reduces neural activation and dopamine release within the mesocorticolimbic reward circuit—a proposed mechanism for its effects on drug motivation—little is known about its central effects in humans. Here, we examined the effects of baclofen on resting cerebral blood flow (CBF) in 19 cocaine-dependent men. Based upon our recent work in nicotine and cocaine-dependent individuals, we hypothesized that baclofen would reduce resting CBF in reward-related brain regions. Further, to investigate the potential functional significance of such changes, we examined whether resting CBF in these regions was related to mesocorticolimbic activation induced by exposure to cocaine cues.
Methods: Participants were randomized to receive baclofen (20 mg t.i.d.; $n=9$) or placebo ($n=10$) and were scanned between days 7–10 of treatment. Continuous arterial spin labeled (CASL) perfusion fMRI was used to measure CBF in the brain at rest; event-related BOLD fMRI was used to measure brain responses to brief cocaine-related and comparison cues. Resting CBF was compared between baclofen- and placebo-treated patients in *a priori* brain regions of interest (ROIs), including the ventral striatum (VS), amygdala (AMYG), medial orbitofrontal (mOFC), and lateral orbitofrontal cortex (lOFC). Regression analysis was used to examine correlations between resting CBF values in these regions and the brain responses to (33msec) cocaine cues.
Results: Resting CBF was significantly lower in the VS of baclofen- than placebo-treated participants ($p<0.05$, uncorrected); no differences between groups were noted in any other regions examined. For the placebo group, cue reactivity in AMYG was *positively* related to resting CBF (in VS, mOFC and LOFC), while cue reactivity in mOFC was *inversely* related to resting CBF (VS, AMYG, LOFC). For the baclofen group, these correlative relationships, in both directions, were attenuated.
Conclusions: These results indicate that baclofen may reduce resting blood flow in the ventral striatum—a critical region involved in drug reward, reinforcement and drug-seeking. The predictive relationships between resting CBF and limbic cue reactivity in placebo patients suggest that the brain at rest may influence drug-motivated behavior/relapse vulnerability. Baclofen attenuated these relationships, and this capability may be tied to its therapeutic potential. Together, these data highlight important relationships between the resting and 'task-activated' brain, and they underscore the potential utility of baclofen as a medication for the treatment of cocaine dependence.
Keywords: fMRI, baclofen, GABA B agonist, resting state, cue reactivity
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M106. 'Trouble Waiting to Happen'? Heightened Striatal Resting Perfusion in Cocaine Patients Predicts Limbic Vulnerability to Drug Cues

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Background: We recently found that cocaine inpatients with a heightened brain response to very brief cocaine (and sexual) cues in reward-relevant regions (e.g., ventral striatum/ventral pallidum/amygdala) relapsed to drug use more rapidly than those without this biomarker. As the brain's resting state can sometimes be used to detect pathologies, *even without the use of a task or probe*, we examined whether cocaine patients' resting activity in ventral striatum (and other reward-related regions) might predict the subsequent brain response to provocative drug cues. Our hypothesis was that patients with an elevated resting perfusion in motivational circuitry—indexing a higher basal rate of neuronal firing—might have a motivational system that is especially vulnerable to evocative cues: 'trouble waiting to happen'. Demonstrating a strong predictive relationship between activity in resting vs. cue-triggered motivational circuits would have mechanistic, theoretical and practical implications for our understanding, and treatment, of relapse vulnerability.
Methods: We studied a new cohort ($n=20$; ongoing) of cocaine-dependent patients; these patients were participants in a large ongoing study focused on brain predictors of relapse. As part of their study participation, each individual received a functional magnetic resonance imaging (fMRI) session with initial resting scans, followed by task-related acquisitions. For the **resting perfusion** data described here, we collected a 5-min Pseudo-continuous Arterial Spin-Labeled (PCASL) scan, which yields an estimate of cerebral blood flow (CBF; ml/100 g tissue /minute) at each brain voxel. For the **cue task** data, we administered an event-related BOLD (Blood Oxygen-Level-Dependent) fMRI task to measure the brain response to (24 unique cues per category) cocaine-related and comparison (sexual, aversive or neutral) visual cues of 500 msec duration. Average interstimulus interval was 1500 msec (TR = 2 sec). Data were smoothed, normalized, realigned and batch-analyzed within SPM 8, using canonical HRF as the basis function. Pre-planned contrasts compared the brain response to evocative (e.g., cocaine) vs. neutral cues. For the correlational analyses, the mean resting CBF for a given anatomical region of interest (e.g., ventral striatum VS; amygdala, AMYG; medial orbitofrontal cortex, MOFC, lateral orbitofrontal cortex, LOFC; and anterior insula, INS, as provided by the Harvard—Oxford brain atlas) was used as a single regressor against the drug cue contrast (cocaine cue-neutral cue, first 24 repetitions). The resulting 5 statistical parametric maps were thresholded at $2>t<5$ for display, and for generating scatterplots.
Results: Prior to conducting correlations, we confirmed that our 500 msec cues (cocaine v. neutral contrast) differentially activated the motivational circuitry (striatum, insula, etc). Consistent with our hypothesis, higher resting perfusion (CBF) in the VS indeed predicted a stronger cue-triggered response in r.VS ($r=0.53$; $r2=0.28$), r.AMYG ($r=0.51$; $r2=0.26$), and r.LOFC ($r=0.65$; $r2=0.42$). Resting perfusion in LOFC also predicted cue-triggered activity in r.VS.

and r.LOFC (r values < 0.4). Intriguingly, though not part of our initial hypotheses, cue-triggered activity in the inferior temporal region was inversely related to resting perfusion in four of the 5 a priori ROIs ($-0.73 >$ r values $<$ -0.52).

Conclusions: To our knowledge, the findings in this and an additional ACNP presentation (please see Young, *et al*, ACNP 2013) represent the first demonstration of correlations between resting perfusion and a cue-provoked, relapse-relevant brain state in addicted individuals. The results have a number of implications. Mechanistically, these correlations suggest that resting activity (basal firing rate) in the appetitive motivational system may be a 'trait-like' feature, a biomarker of the vulnerability to motivationally significant stimuli. From a theoretical perspective, it will be important to determine whether these correlations are also present in non-addicted populations. From a practical perspective, being able to detect 'trouble waiting to happen' from a resting scan would be very useful research tool, offering a new brain target in medication development for addiction.

Keywords: resting state, resting perfusion, relapse prediction, ventral striatum, amygdala, cue reactivity, reward, motivation

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M107. Test-retest Reliability in Extinction Recall: A Neuroimaging Study of Healthy Adults

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Background: Individuals with anxiety disorders have inappropriate fear responses, which may result from deficits in fear or safety learning. Given extinction-related processes are relevant to exposure therapy, we studied fear and safety learning using fear conditioning, extinction and extinction recall (Britton *et al*, 2011). Individuals with anxiety disorders may have difficulties recalling safety memories repeatedly. To understand these processes better, we investigated stability in behavioral responses and neural activation in extinction recall across two time points.

Methods: Thirteen healthy adults (age $M = 26.43$, $S.D. = 5.22$) completed a differential fear conditioning paradigm followed by extinction. Conditioned stimuli (CS) were two women displaying neutral expressions. One CS was paired with the unconditioned stimulus (US), a fearful face terminating with a loud scream ('screaming lady'). Several weeks later, subjects returned to complete extinction recall in an MRI. Images resembling the CS+ and CS− were presented. Using a 0 (not at all) to 6(extremely) scale, subjects made two judgments: 'How likely was she to scream in the past?', probing explicit memory, and 'How afraid are you now?', probing threat appraisal. A repeat MRI was conducted using the same task 8–12 weeks later. Using corrected $\alpha = 0.05$, we tested the stability of the subjective responses to CS+ vs. CS− across the two times points using Pearson correlations. Significant intra-class correlations within AFNI were found after using a threshold of $ICC > 0.56$ and 20 contiguous voxels.

Results: The difference in behavioral ratings of the CS+ and CS− were calculated for the two judgments during extinction recall. At both visits, subjects reported the CS+ was more likely to scream than the CS− (visit 1 $p < 0.016$, visit 2 $p < 0.036$); but were not differentially afraid (both $p > 0.05$). Explicit memory difference scores were correlated across both visits ($r = 0.956$, $p < 0.001$); however, no significant correlations were found for threat appraisal ($r = 0.282$, $p > 0.3$). During explicit memory, neural stability in response to CS+ versus CS− was detected in parahippocampal gyrus [(−26, -9, −26), ICC = 0.95, 241 voxels; (29, −19, −21), ICC = 0.9, 121 voxels)], inferior frontal gyrus/BA47 [(54, 29, −6), ICC = 0.86, 233 voxels], and insula [(−29, 19, 4), ICC = 0.78, 30 voxels]. During threat appraisal, neural stability was detected in the ventromedial prefrontal cortex [(14, 44, −6), ICC = 0.76, 40 voxels; (1, 64, −4), ICC = 0.87, 34 voxels].

Conclusions: In this preliminary analysis, the behavioral response for explicit memory was stable over time in healthy adults, possibly due to stability within activation of neural circuitry supporting explicit memory. In addition, ventral prefrontal cortex regions showed stability in threat appraisal, though behavioral responses were not correlated. In healthy adults, increased stability may be detected in the explicit memory condition rather than threat appraisal as these individuals did not rate high levels of fear at either visit. Understanding stability in behavioral and neural responses to extinction recall will provide further insight into treatment studies using this paradigm.

Keywords: Fear conditioning, reliability, fMRI

Disclosures: J. Britton, Nothing to Disclose; C. Spiro, Nothing to Disclose; T. Shechner, Nothing to Disclose; G. Chen, Nothing to Disclose; D. Pine, Nothing to Disclose.

M108. Hippocampal and Amigdala Volume Increase in Lithium-treated Bipolar I Patients Compared with Unmedicated Patients and Healthy Subjects

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Background: The neuroimaging studies in Bipolar Disorder (BD) have shown neuroanatomical changes in gray matter within the anterior limbic network, including prefrontal, medial temporal and subcortical structures. Some authors claim that the psychotropic drugs commonly used to treat BD, including lithium, may modify the neuroanatomical abnormalities associated with the disorder. Previous studies have associated the increase of the volume of the Amygdala and Hippocampus with the neurotrophic effects of lithium.

Methods: 32 euthymic BID patients (16 on lithium monotherapy for at least 2 years and 16 without medication for at least 2 months previous to the evaluation), and 20 healthy control subjects (all right-handed, with no history of

other psychiatric/neurologic diagnoses, electroconvulsive therapy, encephalocranial trauma nor substance abuse and free of benzodiazepine use for at least 6 months), where evaluated in a descriptive-correlational, cross-sectional study that used MRI to identify comparative volumetric changes in the Amygdala and hippocampus.
Results: Significant differences among the three groups were found in left amygdala volume, right amygdala volume and left hippocampus volume. Lithium-treated BD patients differ significantly from healthy controls regarding the volumes of the same areas: left amygdala ($p = 0.016$), right amygdala ($p = 0.016$) and left hippocampus ($p = 0.007$). However, lithium-treated and unmedicated bipolar patients differ only in the volume of the left amygdala ($p = 0.001$).
Conclusions: Our study showed important volumetric changes of the Amygdala and hippocampus of Lithium treated patients, mainly in left amygdala and according with previous results about the neurotrophic effects of lithium. Control of confounding factors make it likely to be an effect produced by medication, nevertheless, further studies and a larger population are needed in order to establish a statistically significant difference and reinforce these findings
Keywords: neuroimaging, bipolar disorder, lithium therapy
Disclosures: C. Lopez-Jaramillo, Nothing to Disclose; C. Vargas Upegui, Nothing to Disclose; J. Palacio, Nothing to Disclose; G. Castrillon, Nothing to Disclose; E. Vieta, ; C. Bearden, Nothing to Disclose; S. Fears, Nothing to Disclose; N. Freimer, Nothing to Disclose; J. Escobar, Nothing to Disclose.

M109. Greater Translocator Protein (TSPO) Distribution Volume during Major Depressive Episodes of Major Depressive Disorder

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Background: Over the past three years, new advances in radioligand development for positron emission tomography (PET) now enable imaging of TSPO V_T, an index of translocator protein levels. Translocator protein levels are elevated when microglia are activated during inflammation. While it is unclear whether neuroinflammation occurs in the brain during major depressive episodes (MDE) secondary to major depressive disorder (MDD), greater cytokine levels have been frequently reported in the plasma during MDE and environmental influences that raise cytokines are associated with depressed mood.
Methods: [^{18}F] FEPPA PET was applied to measure TSPO V_T in the prefrontal cortex, anterior cingulate cortex and hippocampus in MDE ($n = 10$) secondary to MDD and health ($n = 10$). All subjects were drug and medication free, non smoking and had no additional psychiatric or medical illnesses. Cases and controls were matched for alleles of the rs6971 polymorphism which influences binding of [^{18}F]FEPPA (as well as virtually all of the newest generation of PET radiotracers) to TSPO.
Results: TSPO V_T was elevated in MDE in the prefrontal cortex, anterior cingulate cortex, and hippocampus by 24%, 21% and 25% respectively (analysis of variance for each region: effect of MDE versus health: $F_{1,17} = 3.5$ to 4.5, $p = 0.05$, 0.08 and 0.05; effect of genotype: $F_{1,17} = 11.2$ to 12, $p = 0.004$, 0.003 and 0.003 respectively).
Conclusions: To the best of our knowledge this represents the first positive finding in support of greater neuroinflammation in the brain in MDE since the most likely explanation for greater TSPO V_T in the prefrontal cortex, anterior cingulate cortex and hippocampus is that this reflects the presence of activated microglia from neuroinflammation. This argues for further development of anti-inflammatory treatments for MDE secondary to MDD.
Keywords: neuroinflammation, major depressive disorder, translocator protein, positron emission tomography
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M110. Distinct Patterns of Functional Connectivity in Patients with Childhood-Onset Schizophrenia, Their Unaffected Siblings, and Healthy Controls

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Background: Childhood-onset schizophrenia (COS) is a rare, devastating form of the disease, defined by the onset of psychosis before the age of 13. Previous studies from our laboratory have identified the hippocampus as a site of structural abnormality in COS (Nugent *et al.* 2007, Mattai *et al.* 2011), in keeping with evidence for hippocampal dysfunction in schizophrenia (e.g. Tamminga *et al.* 2010, Lodge and Grace, 2013). In a recent investigation of hippocampal subregions, we found that structural changes were most salient in the anterior hippocampus, where probands showed marked deformations that were also detectable, albeit less pronounced, in unaffected siblings (Johnson *et al.* 2013). The shared nature of these structural alterations suggests that they represent a possible trait marker for schizophrenia. In the present study, we used resting-state fMRI to explore the functional significance of these structural changes. We addressed two questions: 1) does the hippocampus have altered functional interactions with specific cortical or subcortical structures in COS? and 2) if so, are these functional alterations shared by healthy COS siblings?
Methods: We acquired whole-brain echo-planar images at 3 T in three groups: COS ($n = 14$), non-psychotic COS siblings ($n = 16$) and healthy volunteers ($n = 24$). Groups did not differ significantly for age, sex, or handedness (all comparisons $p > 0.14$). Scan duration was five minutes,

during which subjects were instructed to fixate a central crosshair. In the preliminary analysis reported here, we focused on the functional interactions of the left hippocampus, where our previous structural study indicated similar alterations for COS probands and their non-psychotic siblings. For each individual, we computed an average time-series for a left hippocampal seed region and correlated it with the time-series of all other voxels in the brain, in MNI space. We then conducted group-level analyses to search for clusters with significant differences (voxel-wise $p<0.005$) between COS patients and COS siblings compared to healthy controls.

Results: Our preliminary analysis identified several brain regions with altered resting-state hippocampal interactions in COS patients and their siblings. The COS group, compared to healthy controls, showed reduced functional correlations between the left hippocampal seed region and both the cerebellum and precuneus bilaterally. Notably, siblings also had reduced functional connectivity between left hippocampus and the bilateral precuneus; this was the only structure with decreased hippocampal interactions in siblings compared to controls. The COS and sibling groups each showed selective cortical regions with *increased* functional connectivity with the hippocampus, relative to controls. These regions were found unilaterally within the same hemisphere (left) as our focused hippocampal seed. The COS group showed increased functional connectivity in the left superior temporal gyrus, whereas siblings showed an increase in the left inferior frontal gyrus.

Conclusions: Our current findings bolster the hypothesis that hippocampal dysfunction plays a key role in the pathophysiology of schizophrenia, and further suggest that, within specific circuits, its dysfunction may represent an endophenotype for the disease. Of primary interest is the observed decrease in hippocampal-precuneus connectivity, which was shared by COS probands and siblings. The precuneus is commonly considered to be part of the 'default mode network' and likely participates in memory retrieval (Cavanna and Trimble, 2006). The decreased precuneus-hippocampal interaction may therefore relate to memory deficits in schizophrenia, and points toward the necessity of continued investigation of shared memory impairments in unaffected siblings. The increased connectivity in COS between left hippocampus and the superior temporal gyrus is also notable, as recent findings suggest its relation to hallucination severity in psychotic individuals (Sommer *et al*. 2012). Together, these findings highlight the potential of using targeted resting-state fMRI, in conjunction with behavioral and structural analyses, to elucidate candidate biomarkers for the disease.

Keywords: fMRI, resting-state, psychosis, cortex

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M111. Alterations in Amygdala Functional Circuitry as a Neural Marker of Emotion Dysregulation in Young Children

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Background: A great deal of controversy has surrounded the diagnosis of children with severe, impairing temper outbursts. Some claim that such outbursts reflect a juvenile form of bipolar disorder, with significant implications for prognosis and treatment. We recently found that most young children (5- 9 years old) with extreme outbursts, defined as relatively long and frequent, are most often diagnosed with Attention-Deficit/ Hyperactivity Disorder (ADHD) and/or Oppositional Defiant Disorder (ODD), and not bipolar disorder (Roy *et al*, in press). Some of these children also suffer from chronic irritability or negative mood that does not fit easily into extant DSM-IV categories. In an effort to improve the reliable diagnosis of these youth, DSM-5 established a new diagnosis, Disruptive Mood Dysregulation Disorder (DMDD). In light of increased interest in utilizing biomarkers of behavioral phenotypes to inform, and improve, nosology, the present study uses resting state functional MRI to assess emotion regulation circuitry in young children who exhibit severe temper outbursts. Given the high prevalence of ADHD in this population, we include a psychiatric comparison group of children with ADHD without temper outbursts, as well as a healthy comparison group. We hypothesize that amygdala-prefrontal circuits involved in emotion regulation will be altered in children with extreme outbursts, as compared to both comparison groups.

Methods: Data collection is ongoing. Three groups of children (ages 5- 9 years) were recruited: (1) Children with severe, impairing temper outbursts (in excess of 10 min at least 3 times per week; TO group; $n=23$); (2) children with ADHD without significant temper outbursts (ADHD group; $n=25$); and (3) healthy children with no psychiatric concerns (HC group; $n=15$). Participants completed a clinical evaluation including the K-SADS-PL and measures of emotion regulation. Following this assessment, eligible participants completed an MRI scan session including a 6-min rest scan (e.g., lie still with eyes open) and a high resolution anatomical scan for registration purposes. Whole-brain analyses were similar to those used in prior studies of amygdala functional connectivity (e.g., Roy *et al*, 2013). For these initial analyses, we analyzed the intrinsic functional connectivity (iFC) of the total left and right amygdala. A time series was obtained for each ROI and correlations were calculated between these time series and every other voxel in the brain, resulting in individual correlation maps which were then converted to Z-value maps using Fisher's r-to-z transformation, and transformed into MNI152 2 mm standard space. Group comparisons were conducted using FLAME, a mixed-effects model implemented in FSL, controlling for age, gender, mean framewise displacement (participant motion), and the scan used (first or second within the session).

Results: Groups did not differ in age, sex, or movement during the resting state scan. All but one child in the TO group were diagnosed with ADHD and the distribution of ADHD type (73.9% Combined Type, 13% Predominantly Hyperactive Type, and 8.7% Predominantly Inattentive Type) did not differ significantly from the ADHD comparison group. DMDD was only diagnosed in five children from the TO group; most did not exhibit chronic irritability. Group comparisons of amygdala iFC yielded two significant findings. First, the TO group showed negative iFC between

right amygdala and frontal pole; the ADHD and HC groups showed no significant iFC between these regions. Second, iFC between amygdala and precuneus was negative in the TO group, and positive in the ADHD and HC comparison groups. Overall, the TO group showed significant differences in right amygdala iFC while the two comparison groups did not differ.
Conclusions: These findings provide preliminary evidence of a putative pathophysiological mechanism of emotion dysregulation in children that is not a function of ongoing ADHD. Specifically, young children with severe outbursts, most of whom have ADHD, exhibit alterations in amygdala iFC with regions of the frontal pole and precuneus that are not observed in children with ADHD without such outbursts. Due to the low number of DMDD diagnoses, we were unable to examine how amygdala circuitry may be different for children with temper outbursts with chronic irritability compared to those with outbursts alone. Further study is needed to directly examine this question.
Keywords: temper outbursts, ADHD, children, intrinsic functional connectivity
Disclosures: A. Roy, Nothing to Disclose; R. Klein, Nothing to Disclose; C. Kelly, Nothing to Disclose; F. Castellanos, Nothing to Disclose.

M112. Fear-potentiated Startle during Extinction Is Associated with Alterations in White Matter Connectivity

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Background: Pathological anxiety has been linked to deficits in extinction of learned fear responses. A network of brain regions participate in extinction learning, including the hippocampus and medial prefrontal cortical regions, particularly, rostral aspects of the anterior cingulate cortex (ACC; Milad *et al*, 2007). The hippocampus is involved with contextual aspects of fear extinction and has reciprocal connections to the ACC, which regulates inhibition of conditioned fear responses during extinction. Functional connectivity studies suggest that greater temporal coupling of hippocampus and ACC activation is associated with efficient extinction of conditioned fear-related responses (Lang, 2009). It is possible that the strength of white matter connections between these regions influence these functional outcomes; however, no studies have examined the relationship between hippocampus/ACC white matter structural connectivity and extinction. This was the objective of the present study.
Methods: Forty-one African American women aged 21 to 62 years with varying degrees of post-traumatic stress disorder (PTSD) symptoms were recruited from an ongoing study of PTSD risk. Current PTSD symptoms, measured with the PTSD Symptom Scale (PSS), were used as a covariate for statistical analyses. Fear-potentiated startle responses (measured using electromyography of the of the right *orbicularis oculi* muscle) were examined during a fear acquisition and extinction paradigm. Diffusion-weighted images were acquired on all participants using Diffusion Tensor Imaging (DTI). Using probabilistic tractography methods (probtrackx, as implemented in FSL; Behrens *et al*, 2007), probabilistic tracts between the bilateral hippocampi and ACC were constructed for each individual and thresholded by 10% to reduce the likelihood of including irrelevant tracts. The cingulum, which represents the primary white matter connection between both hippocampi and the ACC, was used as an anatomical waypoint for these analyses. Mean fractional anisotropy (FA) values were obtained from probabilistic pathways to measure connectivity. Correlational analyses were conducted with path FA values and amplitude of startle response during fear acquisition and extinction; a threshold of $p<0.05$ was employed to define statistical significance.
Results: Bivariate correlational analyses revealed a significant positive correlation between cingulum FA and startle response during early extinction: $r(41)=-0.34$, $p=0.03$. This association became more statistically significant after controlling for age and current PTSD symptoms [$r(41)=-0.41$, $p=0.01$]. No significant correlations were observed between cingulum FA and fear acquisition or late phases of extinction.
Conclusions: We observed that higher fear-potentiated startle responses during the early phase of extinction were associated with poorer structural connectivity between the hippocampus and ACC, even after controlling for variance associated with age and PTSD symptoms. It is possible that the strength of white matter connections in the cingulum influence individuals' ability to efficiently extinguish heightened fear responses during early extinction (termed fear load: Fani *et al*, 2011; Norrholm *et al*, 2011). Structural decrements in this pathway may represent a source of vulnerability for extinction deficits, which characterize anxious pathology.
Keywords: Fear-potentiated startle; extinction; white matter; probabilistic tractography; anxiety
Disclosures: N. Fani, Nothing to Disclose; T. King, Nothing to Disclose; A. Srivastava, Nothing to Disclose; R. Brewster, Nothing to Disclose; S. Norrholm, Nothing to Disclose; K. Ressler, Nothing to Disclose; T. Jovanovic, Nothing to Disclose.

M113. Diffuse Tensor Imaging-based Brain Signatures Accurately Discriminate a Functional Pain from Health: Examining Central Mechanisms in Visceral Pain

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Background: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain or discomfort associated with a change in stool frequency. The prevalence rate of this functional disorder is 10–15% in North America and Europe. IBS is comorbid with other functional somatic syndromes including fibromyalgia, chronic fatigue syndrome, chronic headache, temporal mandibular disorder, and chronic pelvic pain. The pathophysiology of IBS is incompletely understood, however evidence strongly suggests dysregulation of the brain-gut

axis and the involvement of both central and peripheral mechanisms.
Aim: Application multivariate pattern analysis/recognition methods from machine-based learning to analyze large-scale neuroimaging-based structural and anatomical connectivity data to provide new mechanistic insights into IBS.
Hypothesis: Structural and anatomical brain signatures can discriminate IBS patients from healthy controls.
Methods: Structural and diffusion tensor imaging (DTI) brain images were obtained from 52 controls (29 F) and 42 IBS (25 F). Segmentation and regional parcellation was performed using Freesurfer on the UCLA Laboratory of Neuroimaging pipeline using the Destrieux atlas and 7 subcortical regions yielding 165 regions. For each cortical region measures of gray matter morphometry (volume, mean curvature, surface area and cortical thickness) were computed. Deterministic tractography using the Runge-Kutta algorithm was then performed using TrackVis to provide a measure of relative fiber density between regions (Irimia *et al*, NeuroImage, 2012). Each subjects connectivity matrices were concatenated and entered as the data matrix into a sparse Partial Least Square-Discrimination Analysis (Le Cao *et al*, Bioinformatics, 2011).
Results: DTI-based classifier with two components/brain signatures comprising 20 connectivities each achieved greater than 90% accuracy in discriminating IBS from controls based on 10 fold cross-validation performed 10 times and leave-one-out cross validation. Both signatures were primarily comprised by insular, cingulate, frontal, and subcortical (amygdala, brainstem, basal ganglia, thalamus) connectivity. The two signatures accounted for 68% of the variance in the data set (Component 1, 50%, Component 2, 18%). Binary classification measures including sensitivity, specificity, negative predictive value, and positive predictive value were greater than 95%. Classification based on gray matter morphometry was less impressive yielding classification accuracy of 78%.
Conclusions: The regions identified as having altered connectivity in IBS have also shown difference in HC-IBS comparisons of resting state and task based function and morphometry. Results suggest classification algorithms based DTI-based connectivity can be used to identify specific central targets for further pathophysiological investigations targeting treatment of IBS.
Keywords: multivariate pattern analysis, machine learning, neuroimaging, functional, pain,
Disclosures: J. Labus, Nothing to Disclose; J. Van Horn, Nothing to Disclose; C. Torgerson, Nothing to Disclose; C. Ashe-McNalley, Nothing to Disclose; A. Irimia, Nothing to Disclose; M. Chambers, Nothing to Disclose; A. Gupta, Nothing to Disclose; K. Tillisch, **Part 4:** DANONE RESEARCH; E. Mayer, Nothing to Disclose.

M114. Clinical and Neuropsychological Correlates of DTI-derived Connectome Structure in Euthymic Bipolar I Disorder

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Background: Here, we used a novel computational technique and investigated the modular architecture of DTI-derived brain connectomes using a sample of 25 euthymic bipolar I subjects versus 25 gender- and age-matched healthy controls. This novel technique, which we termed the path length associated community estimation or PLACE, utilizes a graph-theoretical metric that measures the difference between inter-modular versus intra-modular path lengths. PLACE consists of the following: (1) extracting modular architecture using top-down hierarchical binary trees, where a branch at each bifurcation denotes a collection of nodes that form a module, (2) constructing and assessing mean modular architecture, and (3) detecting node-level modular changes between groups.
Methods: We scanned 25 healthy subjects (13M/12F; age: 42.2 +/-10.8 years) and 25 gender- and age-matched bipolar subjects (14M/11F; age: 41.7 ± 12.6 years). All bipolar subjects received comprehensive psychiatric evaluations using the structured clinical interview for DSM disorders and met the DSM IV criteria for bipolar I disorder. Additionally, all subjects underwent a battery of comprehensive neuropsychological testing, designed to probe key cognitive domains including working memory, information processing speed, and executive function. At the time of image acquisition, all subjects have been in a euthymic state for at least 30 days. A Siemens 3 T Trio scanner was used to acquire the brain magnetic resonance imaging (MRI) data. High-resolution T1-weighted images were acquired with MPRAGE sequence (FOV = 250 by 250 mm; TR/TE = 1,900/2.26 ms; flip angle = 9 degrees; voxel size = 1 by 1 by 1 mm). Diffusion weighted (DW) images were acquired using SS-SE-EPI sequences (FOV = 190 by 190 mm; voxel size = 2 by 2 by 2 mm; TR/TE = 8,400/93 ms; 64 gradient directions with a b value of 1,000 s/mm2; one minimally diffusion-weighted b0 image). At the time of the MRI scan, seven participants were on valproic acid, one on carbamazepine, three on lamotrigine, 14 on antipsychotic medications, eight on SSRI antidepressant medications, five on other antidepressant medications, and three on benzodiazepines. None of the study participants was on lithium; two participants were not on any psychotropic medications either at SCID or at the time of the MRI scan. To generate structural brain networks, we used a pipeline that integrates multiple image analysis steps. First, DW images were eddy current corrected using FSL (http:www.fmrib.ox.ac.uk) by registering all DW images to their corresponding b0 images with 12-parameter affine transformations. This was followed by the computation of diffusion tensors and then deterministic tractography using fiber assignment by continuous tracking algorithm built into the DTISTUDIO program (maximum bending angle: 60 degrees; FA cutoff: 0.25). T1-weighted images were used to generate label maps using the FREESURFER software (http:surfer.nmr.mgh.harvard.edu). Weighted brain networks formed by the 82 cortical/subcortical gray matter regions were generated using an in-house program in MATLAB by counting the number of fibers connecting each pair of nodes. We then computed connectome metrics including the characteristic path length, global efficiency, and global clustering coefficient. Additionally, we also calculated the inter-hemispheric path length and efficiency as well as the nodal consistency metric V (defined for each

of 82 nodes). For each node, V measures how the modular architecture of a subject's connectome differs from that of the mean connectome computed using the 25 healthy controls (see Gadelkarim 2012 *et al* for details).
Results: Neuropsychological testing revealed significantly impaired working memory in the bipolar group relative to the control group, as measured using the Wechsler Memory Scale (WMS)-symbol span (raw score 27.9 + /- 1.7 in control and 20.9 + /-1.7 in bipolar, $p = 0.004$ after controlling for age and years of education). For correlations, after combining both bipolar and control subjects and controlling for age, gender and years of education, inter-hemispheric path length is significantly negatively correlated with Stroop inhibition/switching performance (measured in seconds, the time needed to complete the task). The Stroop task is an executive function test that assesses selective attention and response inhibition. Here, the longer the connectome's inter-hemispheric path length was, the longer it took the subject to perform the Stroop task. Lastly, in the bipolar group the nodal consistency metric V was negatively associated with the number of depressive episodes for the left isthmus cingulate ($r = -0.493$, $p = 0.017$) and left precuneus ($r = -0.448$, $p = 0.032$).
Conclusions: To conclude, our study represents the first correlation study that investigates the relationship between connectome metrics and clinical and neuropsychological data. Future studies are thus urgently needed to further investigate the utility of these connectome measures and their translational implications. Reference: A framework for quantifying node-level community structure group differences in brain connectivity networks. GadElkarim JJ, Schonfeld D, Ajilore O, Zhan L, Zhang AF, Feusner JD, Thompson PM, Simon TJ, Kumar A, Leow AD. Med Image Comput Comput Assist Interv. 2012;15(Pt 2):196–203.
Keywords: DTI, connectome, graph theory, bipolar i, neuropsychological testing
Disclosures: A. Leow, **Part 2:** In addition to receiving salary from the University of Illinois, I receive(d) income from Community Psychiatry in California, through clinical services as an outpatient psychiatrist.; O. Ajilore, Nothing to Disclose; J. Gadelkarim, Nothing to Disclose; J. Feusner, Nothing to Disclose; T. Moody, Nothing to Disclose; A. Kumar, Nothing to Disclose; L. Altshuler, **Part 1:** Dr. Altshuler has received past funding from Takeda Pharmaceuticals North America, Inc., and H. Lundbeck A/S (advisory board honoraria, October 2012); and Sunovion Pharmaceuticals Inc. (advisory board honoraria, Jan 2013).

M115. Intrinsic Hippocampal Activity as a Biomarker for Cognition and Symptoms in Schizophrenia

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Background: Identification of biomarkers for cognitive dysfunction in schizophrenia is a priority for neuropsychiatric research. Functional imaging studies suggest that intrinsic, 'resting state' hippocampal hyperactivity is a characteristic feature of schizophrenia. The relationships between this phenotype and symptoms of the illness, however, are largely unexplored. In the present study, we examined the relationship between intrinsic hippocampal activity and cognitive function in schizophrenia patients as measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery.
Methods: 28 patients (20 M, 8 F) underwent functional 'resting state' scanning on a 3 T MR system. Hippocampal activity was extracted by group independent component analysis. Correlation analyses were used to examine the relationship between hippocampal activity and scores on the MATRICS Consensus Cognitive Battery, as well as to positive and negative symptoms.
Results: A significant negative correlation was observed between right hippocampal activity and composite MATRICS T-score. Significant negative correlations with hippocampal activity also were observed on the MATRICS domains of Attention/Vigilance, Working Memory, and Visual Learning. Hippocampal activity was positively correlated with total score on the Scale for the Assessment of Negative Symptoms. MATRICS scores were inversely correlated with negative symptoms.
Conclusions: These findings suggest that intrinsic hippocampal activity is broadly associated with cognitive dysfunction in schizophrenia, and support hippocampal activity as a candidate biomarker for therapeutic development.
Keywords: Schizophrenia, Hippocampus, Resting State, Cognition, fMRI
Disclosures: J. Tregellas, Nothing to Disclose; J. Smucny, Nothing to Disclose; J. Harris, Nothing to Disclose; A. Olincy, Nothing to Disclose; R. Freedman, Nothing to Disclose.

M116. Morphometric and Volumetric Subcortical Differences in Alcoholics with and without Comorbid Drug Use Disorders

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Background: Several studies have investigated subcortical atrophy in alcoholics. Reductions in amygdala, hippocampus, and ventral striatum volumes have been reported (Wrase *et al*, 2008). Additional studies have observed volume reductions in the right nucleus accumbens, which was partially ameliorated with increasing days of abstinence (Makris *et al*, 2008). Individuals with alcohol use disorders (AUD) frequently have comorbid substance use disorders. Findings from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) reported that 29% of subjects with an AUD had used other drugs and one-eighth of people with an AUD had a comorbid drug use disorder (DUD) (Falk *et al*, 2008). Subcortical volume reductions have been investigated in alcoholics with psychiatric comorbidity. This study sought to investigate subcortical volume and morphometric differences in alcoholics with and without DUDs.
Methods: Subjects (36 alcoholics without comorbid substance abuse, 93 alcoholics with comorbid substance abuse, 69 healthy controls) underwent a T1-weights structural MRI

on a 1.5 T GE scanner. The structural images were analyzed using FSL-FIRST, a model-based segmentation and registration tool (Patenaude *et al*, 2011). Morphometric differences were analyzed using FSL's Surface-based Vertex Analysis. Results were corrected for multiple corrections using a false discovery rate. Individual subcortical region volumes were outputted using fslstats and were analyzed using JMP SAS. Age, years of education, and intracranial volume (ICV) were used as covariates in all of the above analyses.

Results: When comparing all alcoholics relative to healthy controls, morphometric differences were found in the brain stem ($p = 0.009$), left amygdala ($p = 0.001$), right nucleus accumbens ($p = 0.029$), and right putamen ($p = 0.006$). Morphometric differences were also seen in alcoholics with comorbid DUDs relative to healthy controls in the following regions: brain stem ($p = 0.008$) and right pallidum ($p < 0.001$). In addition, differences were detected in alcoholics without comorbid DUDs relative to healthy controls in the following regions: brain stem ($p = 0.003$) and right nucleus accumbens ($p = 0.042$). Finally, in alcoholics without comorbid DUDs compared with alcoholics with comorbid DUDs differences were seen in the right palladium ($p = 0.015$) and left pallidum ($p = 0.004$). Complementary to morphometric analysis we also made structural volumetric comparisons. Healthy controls had significantly larger regional volumes in the right thalamus ($p = 0.009$) and the right nucleus accumbens ($p = 0.009$). Only the right amygdala showed volumetric reductions in alcoholics with comorbid DUD compared to healthy controls ($p = 0.029$). Healthy controls had significantly larger volumes compared to alcoholics without a DUD in several regions including: left putamen ($p = 0.010$), right putamen ($p = 0.005$), and right pallidum ($p = 0.026$). Additionally there was an interaction between group and education bilaterally in the hippocampus, right ($p = 0.007$) and left ($p = 0.006$).

Conclusions: Several of the regions found to have morphometric and volumetric differences in alcoholics with and without comorbid DUDs are involved in reward processing, including the right nucleus accumbens, left amygdala, and right putamen. Alcohol and drug use disorders have been associated with altered reward processing (Bjork *et al*, 2008). In accordance with results from our previous study, we found more regions with subcortical volume reductions in the alcoholics without a DUD than in the alcoholics with a DUD, both relative to healthy controls. While there were no significant differences in self reported history of alcohol use in the two alcohol groups, the alcoholics with DUDs may have actually consumed less alcohol, because they had other ways of reaching an intoxicated state. Another possibility is the potentially neuro-protective effects of cannabinoids acting through the CB_2 receptor, which has previously been shown to be anti-inflammatory (O'Sullivan and Kendall, 2010).

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Keywords: subcortical, morphometry, substance-abuse, alcoholism

Disclosures: E. Grodin, Nothing to Disclose; R. Momenan, Nothing to Disclose.

M117. A Preliminary Comparison of Methodologies for Quantifying Brain Gamma-Aminobutyric-Acid Concentrations In Vivo using Proton Magnetic Resonance Spectroscopy

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Background: Gamma-Aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the mammalian central nervous system. Disruptions in GABA transmission have been implicated in a number of psychiatric disorders, including substance use and mood disorders. Proton Magnetic Resonance Spectroscopy (1H-MRS) allows for in vivo estimation of brain GABA concentrations via specialized acquisition and post-processing routines, each with their own strengths and weaknesses. The purpose of the present investigation was to compare three specialized 1H-MRS GABA quantification methods in a small group of healthy control subjects.

Methods: Five healthy controls (100% Caucasian, 60% female, *M* age = 28.8 years [*SD* = 6.61], and *M* education level = 16.4 years [SD = 0.89]) completed a Magnetic Resonance Imaging scan (2.9 Tesla field strength), including localized two-dimensional j-resolved (2DJ) and MEGA-PRESS acquisition sequences, with acquisition order counterbalanced between participants, applied to a 30x25x22 mm voxel in ventral anterior cingulate cortex. 2DJ data were post-processed using established Prior Knowledge Fitting methods and MEGA-PRESS data were post-processed using both a validated in-house approach (i.e., a Gaussian line shape was fitted to the GABA 3.0 parts per million resonance in the time-domain, and the integral calculated following fast Fourier transform of the time-domain envelope) as well as the operator-independent LCModel version 6.3 software. Across all 3 acquisition/post-processing methods, GABA estimates had Cramer Rao lower bounds < 20%, and GABA was expressed normalized to creatine (Cr). Bivariate scatterplots, pearson correlations,

and r-squared estimates were produced for each of the 3 possible pairs of acquisition/post-processing methodologies.
Results: GABA/Cr estimates via: 1) LCModel processed MEGA-PRESS were $M = 0.24$, $SD = 0.04$, 2) in-house processed MEGA-PRESS were $M = 0.30$, SD = 0.07, and 3) ProFit processed 2DJ were M = 0.15, SD = 0.04. Associations between GABA/Cr estimates from the 3 different acquisition/post-processing methods were: 1) LCModel and in-house MEGA-PRESS, $r = 0.84$ ($r^2 = 0.71$), 2) LCModel MEGA-PRESS and ProFit 2DJ, $r = 0.59$ ($r^2 = 0.35$), and 3) in-house MEGA-PRESS and ProFit 2DJ, $r = 0.68$ ($r^2 = 0.46$).
Conclusions: In a small group of healthy control subjects, the present study demonstrated that GABA estimates from LCModel analysis of MEGA-PRESS data were highly correlated with estimates from a traditional in-house analysis approach. The present study also demonstrated moderate correlations between GABA estimates from MEGA-PRESS and 2DJ acquisition sequences. Notably, however, GABA estimates from the in-house MEGA-PRESS analysis were more highly correlated with estimates from the ProFit 2DJ analysis relative to the LCModel MEGA-PRESS analysis. Further research is needed to better understand this pattern of associations, and these results should be considered preliminary until replicated in larger samples.
Keywords: GABA, magnetic resonance spectroscopy, MEGA-PRESS, methods, gamma-Aminobutyric acid
Disclosures: J. Prisciandaro, Nothing to Disclose; A. Prescot, Nothing to Disclose; J. Schacht, Nothing to Disclose; R. Anton, Nothing to Disclose; P. Renshaw, Nothing to Disclose; T. Brown, Nothing to Disclose.

M118. Prefrontal Cortex Activation during Safety Signal Processing in Generalized Anxiety Disorder as a Correlate of Overgeneralization

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Background: Generalized Anxiety Disorder (GAD) is characterized by excessive and uncontrollable worries about a variety of events or activities accompanied by a range of physical symptoms. For anxiety disorders in general, fear conditioning and extinction has long been considered critical for understanding etiology and pathogenesis. However, previous studies rarely demonstrated group differences in discriminative conditioning between anxiety patients and healthy controls [1]. A more robust measure of clinically relevant anxiety seems to be the response to a safe conditioned stimulus (CS-), which in patients is indicative of overgeneralization in the fear response [2]. Such an approach on fear conditioning seems to be particularly promising for investigating GAD; however, there is only limited evidence on the neural correlates of fear acquisition in GAD so far [3]. Therefore, we aimed to investigate the neural responses of GAD patients during fear acquisition and extinction learning with a focus on conditioned overgeneralization.Preliminary data from an ongoing study are reported.
Methods: N = 41 medication-free adults (n = 23 GAD patients and n = 18 healthy controls) were diagnosed by a standardized clinical interview and matched on age, sex, and level of education. Blood oxygen level dependent (BOLD) fMRI data were collected on a 3-T scanner during an event-related fear conditioning/extinction paradigm. Two CS (neutral faces) were presented during habituation, acquisition and extinction phases. During acquisition, one of the CS was paired with the unconditioned stimulus (an aversive scream) by use of a reinforcement rate of 50% (CS +). However, only unpaired CS + trials were included in the analysis. Group differences in safety signal processing (GAD > HC: CS− > $CS-_{Habituation}$) were investigated for the acquisition and extinction phases. All data were preprocessed and analysed with SPM8 (exploratory whole-brain analysis: $p < 0.001$ uncorrected, minimum cluster size of 25 consecutive voxels).
Results: Both groups were comparable on age, sex and level of education. Regarding contingency knowledge, there was a non-significant trend suggesting less contingency knowledge in the GAD patient group. For the acquisition phase, GAD patients compared to healthy controls showed widespread increased activation in the dorsolateral, dorsomedial, and ventrolateral prefrontal cortex, the middle and inferior temporal lobe and the cerebellum. No areas with decreased activation were found. For extinction, a similar but less powerful pattern of activation was detected, with GAD patients again showing increased activation in the dorsolateral, dorsomedial and ventrolateral prefrontal cortex, the middle and inferior temporal lobe and the cerebellum, compared to controls. However, during extinction, GAD patients compared to controls showed decreased activation in the precuneus.
Conclusions: Conditioning paradigms are relevant models for the development and maintenance of anxiety disorders. However, the neural responses underlying these processes are still poorly understood. Here, we demonstrate altered safety signal processing as a neural correlate of central relevance to GAD, as has recently been shown similarly for other anxiety disorders as panic disorder / agoraphobia [4]. In particular, increased prefrontal cortex activation during safety signal processing seems to be present during both acquisition and extinction phases. This pattern might be related to emotion regulation efforts or negative prediction errors [5], but future studies are needed to further investigate the exact role of these areas in GAD fear conditioning processes.
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Keywords: fmri, generalized anxiety disorder, fear learning, extinction

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M119. Longitudinal Change in Amyloid Deposition, Measured by PET and 11-C-PiB, in Older Adults

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Background: PET imaging studies of amyloid-beta (ABeta) consistently demonstrate increases over time in individuals with more than minimal ABeta deposition at baseline imaging. However, longitudinal imaging studies of ABeta have included few serial measurements due to the relatively recent development of in vivo PET radiotracers for ABeta.

Methods: We used PET and Pittsburgh compound B (PET-PiB) to investigate longitudinal changes in ABeta deposition and relation to Apolipoprotein E (APOE) genotype in 113 participants (2 with mild cognitive impairment (MCI) and 2 with Alzheimer's Disease (AD) at baseline) in the Baltimore Longitudinal Study of Aging. Participants (mean baseline age 77.3 SD 8.1) were studied at 1 to 2 year intervals and had up to 7 (mean 2.3 SD 1.6) repeated scans (260 scans total) over up to 8 years since 2005. Dynamic PET images were acquired for 70 min after injection of 11-C-PiB, and distribution volume ratios (DVR) were calculated using a cerebellar gray matter reference region and a simplified reference tissue model (1). Affine registration was used to map the SPM PET template onto each subject's 20-min mean PET-PiB image, and the resulting transformation was used to map the AAL atlas labels (2) onto each subject's PET-PiB DVR image. Mean cortical DVR was calculated as the average of DVR values in superior, middle and inferior frontal and orbitofrontal, superior parietal, supramarginal and angular gyrus regions, precuneus, superior, middle and inferior occipital, superior, middle and inferior temporal, anterior, middle and posterior cingulate regions.

Results: Overall increases in PET-PiB over time in the whole sample were 0.87 % per year ($p < 0.0001$). Individuals with minimal PiB retention at baseline (DVR less than 1.15) tended to remain stable over time. However, individuals with more than minimal PET-PiB retention at baseline (DVR of 1.15 or greater) showed linear increases of 1.83 % per year. With the greater longitudinal follow-up in our current analysis, it is possible to track the initial stages of increasing amyloid deposition in some individuals with initially low levels, including individuals greater than 80 years of age. Moreover, we found a significant effect of APOE genotype on mean cortical DVR, with higher baseline DVR in APOE e4 carriers compared with noncarriers ($p = 0.003$), but no significant effect of APOE genotype on the rate of change over time. Results were unchanged after exclusion of participants with diagnoses of MCI and AD at baseline.

Conclusions: PET-PiB imaging of in vivo amyloid burden is sensitive to even small increases in ABeta deposition over time. Once individuals begin to deposit ABeta, they show linear increases in PiB retention over time. APOE genotype appears to modulate baseline or level of ABeta burden but had no significant effect on rate of progression. This finding is consistent with a robust effect of APOE genotype on overall amyloid burden and less consistent effects of APOE on amyloid progression in prior longitudinal studies. Overall, these results indicate that PET amyloid imaging reliably detects even modest levels of ABeta and change in ABeta deposition, supporting its utility in patient selection and therapeutic monitoring in clinical trials.

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Keywords: amyloid imaging, PET-PiB, preclinical Alzheimer's disease, aging, longitudinal studies

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M120. Global Resting-state fMRI Analysis Identifies Frontal Cortex, Striatal, and Cerebellar Dysconnectivity in Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is associated with regional hyperactivity in cortico-striatal circuits. However, the large-scale patterns of abnormal neural connectivity remain uncharacterized. Resting-state functional connectivity (rs-fcMRI) studies have shown altered connectivity within the implicated circuitry, but they have used seed-driven approaches wherein a circuit of interest is defined *a priori*. This limits their ability to identify network abnormalities beyond the prevailing

framework. This limitation is particularly problematic within the prefrontal cortex (PFC), which is large and heterogeneous and where *a priori* specification of seeds is therefore difficult. A hypothesis-neutral data-driven approach to the analysis of connectivity is vital.
Methods: We analyzed rs-fcMRI data collected at 3 T in 27 OCD patients and 67 matched controls using a recently developed data-driven global brain connectivity (GBC) method, both within the PFC and across the whole brain. Parallel analysis in an independent cohort of adolescents with OCD is ongoing.
Results: We found clusters of decreased connectivity in the left lateral PFC in both whole-brain and PFC-restricted analyses. Increased GBC was found in the right putamen and left cerebellar cortex. Within ROIs in the basal ganglia and thalamus, we identified increased GBC in dorsal striatum and anterior thalamus. In striking contrast, the ventral striatum/nucleus accumbens exhibited decreased global connectivity, but increased connectivity specifically with the ventral anterior cingulate cortex in adults with OCD.
Conclusions: These findings identify previously uncharacterized PFC and basal ganglia dysconnectivity in OCD and reveal differentially altered GBC in dorsal and ventral striatum. Results highlight complex disturbances in PFC networks, which could contribute to disrupted cortical-striatal-cerebellar circuits in OCD.
Keywords: obsessive-compulsive disorder; prefrontal cortex; basal ganglia; resting-state fMRI; global connectivity
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M121. Examining Domains of Borderline Personality Disorder Using MRI

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Background: Borderline Personality Disorder (BPD) is a mental illness of significant impact on the population associated with significant burden, use of services and mortality. Recently, there has been growing interest in understanding the neuroscience underlying domains of functioning within BPD that might serve to guide treatment recommendations. This study utilizes four magnetic resonance techniques to explore the relationship of psychological domains to brain dynamics. This work has the potential to corroborate symptom domains and to better understand their neurophysiology.
Methods: Participants received evaluation of Axis I and II symptoms after responding to announcement of a BPD study of treatment and imaging. All subjects received physical exams and laboratory studies. Twenty-one medication-free BPD subjects (71% female, 29.09 ± 7.45) were compared to 10 similarly aged controls (60% female, 27.01 years old $\pm$ 7.92). MRI acquisitions were performed on a Siemens Trio 3 T scanner at the Center for Magnetic Resonance Research at the University of Minnesota and included: resting state functional magnetic resonance imaging (fMRI), emotion faces fMRI task, diffusion tensor imaging (DTI), and proton magnetic resonance spectroscopy. To evaluate how brain functioning maps on to psychological dimensions, a broad battery of clinical scales were collected including: Symptoms Checklist-90, Zanarini-Borderline Personality Rating Scale, Montgomery Asberg Depression Rating Scale, Barratt Impulsivity Scale, and Sheehan Disability Scale. Imaging measures were compared by group; for measures that had shown a group difference, correlations were performed with clinical measures.
Results: *Resting-state fMRI:* Resting-state functional connectivity was lower in the BPD group in comparison to the control group for the right-hemisphere connections between amygdala and ACC ($p = 0.05$) and between amygdala and OFC ($p = 0.06$). Right amygdala-ACC connectivity was inversely correlated with social anxiety ($r = -0.450$, $p = 0.05$), depression ($r = -0.58$, $p = 0.008$), interpersonal sensitivity ($r = -0.52$, $p = 0.02$), and identity disturbance ($r = -0.46$, $p = 0.04$). Right amygdala-OFC connectivity was inversely correlated with anxiety ($r = -0.45$, $p = 0.05$), depression ($r = -0.49$, $p = 0.02$), affective instability ($r = -0.47$, $p = 0.05$), chronic feelings of emptiness ($r = -0.51$, $p = 0.03$), and interpersonal sensitivity ($r = -0.46$, $p = 0.04$). *Emotion Task:* Amygdala activation in response to fear was greater in the BPD group than in the control group on the right ($p = 0.03$) and on the left ($p = 0.08$). This activation was positively correlated with chronic feelings of emptiness ($r = 0.49$, $p = 0.03$), identity disturbance ($r = 0.49$, $p = 0.03$) and total disability ($r = 0.52$, $p = 0.02$). *DTI:* The BPD group showed significantly higher mean diffusivity ($p = 0.02$) and higher radial diffusivity ($p = 0.03$) than the control group. Both of these measures were positively correlated with the total impulsivity ($r = 0.47$, $p = 0.03$ and $r = 0.52$, $p = 0.02$, respectively), total disability ($r = 0.53$, $p = 0.02$ and $r = 0.46$, $p = 0.04$, respectively), depression ($r = 0.50$,$p = 0.02$ and $r = 0.42$, $p = 0.06$, respectively) and hostility ($r = 0.68$, $p = 0.001$ and $r = 0.63$, $p = 0.003$, respectively). Spectroscopy: ACC concentrations of N-acetyl aspartate (NAA) were lower in the BPD group at a trend level ($p = 0.09$) and were inversely related to non-planning impulsivity ($r = -0.514$, $p = 0.02$) and with affective instability ($r = -0.423$, $p = 0.08$).
Conclusions: The study of domains of BPD using multimodal neuroimaging have confirmed previous findings of identifying differences within fronto-limbic neural networks between patients and controls; however, beyond just comparing subjects, this study illustrates the brain functions associated with domains of BPD. Of note is the replication of previous studies showing brain functional correlations with impulsivity and aggression—two high significant domains. These findings have the potential of combining with the meta-analytic papers noting how BPD domains are associated with medication treatment outcomes and may assist in personalized treatment decisions.
Keywords: borderline, personality, disorder, fmri, DTI

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M122. The Norepinephrine Transporter: A Novel Target for Imaging Brown Adipose Tissue

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Background: Obesity is characterized by a relative impairment of energy expenditure associated with adaptive thermogenesis. Studies in animals have shown that adaptive thermogenesis involves activation of brown adipose tissue (BAT), a tissue previously thought to completely regress in adult humans. Positron emission tomography (PET) scans, verified with tissue biopsy, support the continued existence of BAT in adults. Understanding the extent to which BAT in adult humans plays a role in energy balance and obesity has been limited by the current detection methodology using FDG-PET, which requires cold stimulation. The purpose of this study is to test a new, mechanistically driven approach for imaging BAT in humans that capitalizes on the fact that BAT is strongly innervated and regulated by the sympathetic nervous system (SNS) machinery. More specifically, we propose to image the norepinephrine recycling component, designated the norepinephrine transporter (NET). We hypothesize that the NET-PET imaging approach using (*S,S*)-[^{11}C]O-methylreboxetine) ([^{11}C]MRB), a highly selective NET ligand, will provide a non-stimulated target for BAT that is proportional to BAT mass. In this talk, our evaluation of using [^{11}C]MRB as a tool for NET-PET imaging both preclinical in rats and clinical in humans will be discussed.
Methods: *Preclinical ex vivo and in vivo evaluation in rats of the specificity of [^{11}C]MRB labeling for BAT*: PET images of male Sprague-Dawley rats with [^{18}F]FDG and [^{11}C]MRB were compared. Relative [^{18}F]FDG or [^{11}C]MRB retention at 20, 40 and 60 min post-injection was quantified on awake rats after exposing to cold (4°C for 4 h) or remaining at room temperature (RT). Rats pretreated with unlabeled MRB or nisoxetine 30 min before [^{11}C]MRB injection were also assessed. The [^{11}C]MRB metabolite profile in BAT was also evaluated. *Clinical evaluation in humans of the specificity of [^{11}C]MRB labeling for BAT:* Five healthy, Caucasian subjects (4 male, 1 female; age 23.6 ± 1.8 years; BMI 22.4 ± 2.0 kg/m^2) were recruited. Total body fat and lean body mass were assessed via bioelectrical impedance analysis. Subjects underwent PET/CT imaging using [^{11}C]MRB under RT and mild cold stimulated conditions (Cool vest, with enthalpy of cold packs is rated to be 15°C) compared to [^{18}F]FDG PET/CT imaging at RT and mild cold conditions. Subjects were fasting and received all 4 scans within 4 weeks. Mean standardized uptake value (SUV) for FDG and [^{11}C]MRB, and distribution volume ratio (DVR) for [^{11}C]MRB were estimated via MRTM2 using occipital brain area as the reference region. A ratio of BAT-DVR to muscle-DVR (BAT/muscle) were also computed and compared.
Results: PET imaging demonstrated intense [^{11}C]MRB uptake (SUV of 2.9 to 3.3) in the interscapular BAT of both RT and cold-exposed rats, and this uptake was significantly diminished by pretreatment with unlabeled MRB. In contrast, [^{18}F]FDG in BAT was only detected in rats treated with cold. *Ex vivo* results were concordant with the imaging findings; i.e., the uptake of [^{11}C]MRB in BAT was 3 times higher than that of [^{18}F]FDG at RT ($P = 0.009$), and the significant cold-stimulated uptake in BAT with [^{18}F]FDG (10-fold, $P = 0.001$) was not observed with [^{11}C]MRB ($P = 0.082$). Furthermore, there were no correlations between FDG uptake (either at RT or cold) with BAT mass; whereas there was a good correlation between MRB uptake at RT with BAT mass ($R^2 = 0.945$). HPLC analysis revealed 94–99% of total radioactivity in BAT represented unchanged [^{11}C]MRB. Clinical evaluation: [^{18}F]FDG uptake in BAT was observed in all subjects under mild cold conditions, but not at RT (SUV: RT 0.69 ± 0.08 vs. cold 3.36 ± 2.00). However, [^{11}C]MRB uptake occurred in BAT in the same anatomic locations as seen in the [^{18}F]FDG scans under both RT and cold conditions, and the difference of [^{11}C]MRB uptake between RT and cold was not significant [BAT-DVR: RT 0.91 ± 0.21 vs. cold 1.12 ± 0.35; or DVR (BAT/muscle): RT 2.16 ± 0.66 vs. cold 2.36 ± 0.74]. Furthermore, FDG BAT uptake (SUV) under mild cold correlated with MRB DVR (BAT/muscle) at RT ($\rho = 0.9$, $P = 0.037$).
Conclusions: Both ofour preliminary preclinical and clinical imaging studies have shown that [^{11}C]MRB can efficiently label BAT in rats and humans at both RT and mild cold conditions. In contrast, [^{18}F]FDG labeling of BAT occurred only under mild cold conditions. These preliminary data suggest that [^{11}C]MRB-PET may provide a non-stimulated target for imaging BAT in humans, that appears to be quantitatively proportional to BAT mass. Supported by NIH/NIDDK.
Keywords: Obesity, brown adipose tissue, brown fat, PET, norepinephrine transporter, MRB,
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M123. Measuring Smoking-induced Extrastriatal Dopamine Release: A [11C]FLB-457 PET Study

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Background: Preclinical studies indicate that nicotine can induce dopamine (DA) release in striatal and cortical brain regions, contributing to the reinforcing and cognitive effects respectively. Positron emission tomography (PET) imaging studies using the $D_{2/3}$ radiotracer [^{11}C] raclopride to indirectly measure DA release via receptor occupancy have confirmed that tobacco smoking releases DA in striatal regions in humans. However, due to the low density of DA receptors in the cortex it was not possible to measure

extrastriatal DA release in humans until the recent development of high affinity $D_{2/3}$ radiotracers. In this study we used the high affinity $D_{2/3}$ radiotracer [^{11}C]FLB-457 to index tobacco-induced extrastriatal DA release in smokers.
Methods: Ten nicotine-dependent daily cigarette smokers underwent two high affinity [^{11}C]FLB-457 PET scans: after overnight abstinence and smoking reinstatement (biochemically verified by expired carbon monoxide and plasma nicotine levels). Craving, withdrawal, mood and cognitive performance were assessed under both smoking conditions. Voxel-wise parameter estimation of binding potential (BP_{ND}) was performed using the basis function implementation of SRTM with the tissue time activity curve of the cerebellar cortex as the reference region. Spatially normalized [^{11}C]FLB-457 BP_{ND} maps were statistically investigated to assess significant changes between the two conditions at every voxel using paired-tests (SPM 8). Results from the whole-brain voxel-wise paired t-test (abstinence $>$ smoking) were masked with a map of a-priori regions of interest and subjected to an uncorrected threshold of $p<0.05$, with a minimum 30-voxel cluster extent.
Results: There was a reduction [^{11}C]FLB-457 BP_{ND} following smoking (an indirect measure of DA release) in the dorsolateral prefrontal cortex (dlPFC; 323 voxels, peak $t=3.38$, $p=0.004$), dorsal medial prefrontal cortex/ anterior cingulate cortex (dmPFC / ACC; 1496 voxels, peak $t=5.32$, $p<0.001$), both of which survived a more stringent threshold of $p<0.01$, and the left insula (47 voxels, peak $t=2.54$ $p=0.016$). Exploratory analysis focused on limbic regions identified an effect in the bilateral amygdala (Left: 102 voxels, peak $t=3.28$, $p=0.005$; Right: 108 voxels, peak t $=3.03$, $p=0.007$). Extraction of values from these clusters revealed % changes in BP_{ND} in smoking versus abstinence conditions of -12.0% (SD $=9.4$) in the dlPFC, -11.5% (SD $=12.8$) in the dmPFC/ACC, -7.1% (SD $=7.9$) in the left insula and -13.1% in the bilateral amygdala.
Conclusions: To our knowledge this is the first demonstration of smoking-induced DA release in cortical regions such as the dlPFC, dmPFC and ACC. There was also some evidence for DA release in the insula and amygdala. The dmPFC, ACC, insula and amygdala are regions consistently associated with tobacco cue-presentaton, subjective craving and relapse susceptibility in fMRI studies, while the dlPFC appears to exert top-down control on tobacco craving and is involved in tobacco's pro-cognitive effects. As such [^{11}C]FLB-457 may be a useful tool to investigate individual differences in tobacco addiction severity and treatment response.
Keywords: tobacco, positron emission tomography, cigarette smoking, cortical, dopamine
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M124. A Longitudinal Mentoring and Training Program for Psychiatric Scientists

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Background: There is increasing need for innovative methods to promote training, advancement, and retention of clinical and translational investigators in order to build a pipeline of trainees to focus on mental health-relevant research careers. The specific aim of the Career Development Institute for Psychiatry (MH090947) is to provide the necessary skill set and support to a nationally selected broad-based group of young psychiatrists and PhD researchers in order to launch and maintain successful research careers in academic psychiatry. The program targets such career skills as writing, negotiating, time management, juggling multiple demanding responsibilities, networking, project management, responsible conduct of research, and career goal setting. The current program builds on the previous program by adding a longitudinal, long-distance, virtual mentoring and training program, seen as integral components to sustaining these career skills.
Methods: The program is geared toward individuals at the critical transition point between the completion of research training and initial faculty appointment or very early in the initial appointment. The Career Development Institute (CDI) faculty consists of experts in various fields of psychiatry to reflect the diversity for which we are aiming in the composition of the participants. Peer advisors are selected from previous CDI classes and represent colleagues just a few years ahead of the current class in their research career trajectory. These younger faculty are particularly compelling role models because the trainees may see them as more recently succeeding in the path they themselves are following. The CDI is a multi-faceted, longitudinal training program designed to support and enhance the psychiatric research careers of young investigators. The four-phase, 24-month long program consists of career and skills evaluation (Phase 1), completion of didactic training and materials prior to attendance at a four-day in-person, hands-on workshop with seminars, one-on-one mentoring, and career goal-setting (Phase 2), 20 months of coaching/long-distance mentoring by CDI faculty and the peer advisors, live chats online, and access to an ongoing learning center hosted on a dedicated and secure CDI website (Phase 3), and a follow-up career evaluation after 24 months (Phase 4) and repeated annually. Potential mentors are identified for each participant for long-distance mentoring. Recommendations are based on the career stage of the participant, research interests as described in the application, narrative summary, short- and long-term goals, and specific research interests. The mentors/mentees that are paired in Phase 2 meet online (or use other communication modalities) every two months to review the participant's progress toward the goals that were established by the participant in Phase 1. This is the participant's opportunity to seek continued advice, request critiques on drafts of papers or applications, or work on a scientific collaboration. Each pair schedules the session at their convenience. Participants are required to attend pre-scheduled, one-hour webinars every other month during the 20-month follow-up period via web conferencing. Webinars are online live meetings where all participants can hear the presenter, can contribute to a group discussion (including asking questions), and can view the presentation slides on their computer screen in real-time.

Results: Evaluation of the CDI Class of 2012 experience has been measured by a post workshop survey, mentor/mentee surveys completed after mentoring sessions, post –webinar surveys and 6 month telephone interviews with class participants. Preliminary results after the first 18 months are favorable. The long-distance mentoring program and webinars have been enthusiastically embraced. Most mentees/mentors have rated the sessions 'highly satisfactory.' Many pairs have reported communicating via e-mail in between formal scheduled sessions and several have m et at professional meetings or engaged in other collaborative activities.
Conclusions: We will continue to evaluate and monitor participant satisfaction and recommendations for revisions to the content and strategies for future classes. Such process evaluation is invaluable for us to continually renew, update, and improve the overall CDI curriculum components and methodologies. The longitudinal program of education, training, mentoring, peer support, and communications for individuals making the transition to academic research should increase the number of scientists committed to research careers in mental health.
Keywords: career training, career development, training, mentoring and physician-scientist.
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M125. EEG and fMRI Findings of Reduced Neural Synchronization during Visual Integration in Schizophrenia

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Background: Patients with schizophrenia have well-documented deficits in visual perception that are detectable with a range of paradigms and measurement techniques. One area of visual processing impairment in schizophrenia is integration, the process that incorporates contours present or inferred in a visual stimulus into a coherent shape or object. Aspects of feature binding have been explored with electroencephalography (EEG) techniques. Studies have shown that binding is represented by synchronized neuronal firing in the gamma-band frequency range (generally between 30–70 Hz). Visual integration in schizophrenia has been examined with the use of illusory contours, commonly seen in Kanizsa illusory stimuli. EEG studies have shown that schizophrenia patients have lower amplitude ERPs and lower gamma band intertrial coherence (a measure of neural synchronization) when viewing illusory contour figures compared to healthy controls. These deficits have been hypothesized to reflect a dysfunctional NMDA receptor system. In contrast to the EEG studies, we are not aware of any functional magnetic resonance imaging (fMRI) studies using illusory contour figures in schizophrenia. The current study aimed to examine visual integration in patients with schizophrenia using a multimodal imaging approach.
Methods: Fifty patients with schizophrenia (SZ) and 38 healthy controls (HC) had EEG recorded; 25 SZ and 26 HC had fMRI available for analysis; 24 SZ and 21 HC had both fMRI and EEG data. EEG and fMRI data were recorded in separate sessions. For both EEG and fMRI sessions, participants passively viewed different types of figures: either images (diamond or square) with real contours; illusory contours, or no contours. EEG data were examined in two ways: 1) we examined traditional event-related potential components (ERPs) associated with visual processing (P100, N100, P200); and 2) gamma band (40–60 Hz) intertrial coherence was examined with time-frequency analyses. For fMRI, we focused on activity within the lateral occipital complex, an area that is sensitive to object processing, anatomically defined by the Oxford-Harvard atlas. Finally, we examined correlations between ERP, gamma band coherence and fMRI activity.
Results: For ERPs, there was no significant main effect of group or figure type for the P100. Schizophrenia patients had significantly reduced N100 and P200 amplitudes to all three figure types in comparison to controls. Both groups showed significantly larger N100 responses to illusory and real contour compared to no contour figures. Both groups showed significantly larger P200 responses to real contour compared to illusory and no contour figures. For gamma band coherence, there was a significant group X figure type X region interaction. Controls showed gamma band coherence between 70–100 ms to illusory contours that was significantly larger than that seen in SZ over parieto-occipital and occipital electrodes; coherence was not significantly different between groups for the other two figures types or electrode sites. For fMRI, both groups showed robust activation in the lateral occipital complex for all three types of figures. There were no group or condition main effects in activity within the lateral occipital complex. The ERP and coherence variables of interest were not correlated with percent signal change values extracted from the lateral occipital complex.
Conclusions: This is the first study to our knowledge to examine visual integration in schizophrenia using both EEG and fMRI methodologies. We found the following: First, schizophrenia patients showed reduced ERP amplitudes compared to healthy controls, regardless of the type of contours. Second, schizophrenia patients had significantly less gamma band coherence compared to controls when viewing illusory contours, indicative of a visual integration dysfunction. Third, all participants exhibited robust fMRI activity within the lateral occipital complex, despite the type of contour, and there were no group differences in this region. Finally, fMRI and EEG activity were not correlated in either group. These findings suggest that schizophrenia patients have a specific deficit in gamma band coherence when viewing illusory contours that rely on integration processes. Using a multimodal approach to examine visual integration revealed deficits using one method (EEG) but not the other (fMRI). Deficits in visual integration are seen at the millisecond level when measured with EEG, but not in fMRI given its poorer temporal resolution due to the slow BOLD response.
Keywords: schizophrenia, eeg, fmri, visual, integration.

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M126. Translating Functional Neuroimaging into Clinical Care by Modeling Normative Variance in Cognition and Neural Function: Insights from the Cognitive Connectome

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Background: It is well accepted that as humans we exhibit wide interindividual variation in cognitive ability both between and across cognitive domains. Yet our understanding of the neural information processing correlates of cognitive function is largely represented by group, rather than individual differences research. Moreover, the current brain-behavior relationships representing cognitive ability reflect largely models of functionally segregated brain activations rather than modes of functionally integrated brain activity. The extant group-level model of discrete neuroactivations is inconsistent with the individual patient-level characterization of domain-specific cognitive function common to neuropsychological assessments and cognitive training in clinical settings. This mismatch represents a barrier to the translation of functional neuroimaging approaches such as fMRI into individualized patient care. To address this need, we initiated a project referred to as the 'Cognitive Connectome' to map the normative variance in brain function related to individual variation in ability across multiple domains of cognition assessed in the clinical practice of neuropsychology. This fMRI initiative seeks to map neural responses and function neural processing network connectivity at the single subject level across tasks and to depict the brain-behavior relationships at the level of cognitive task performance.
Methods: The Cognitive Connectome uses direct and conceptual fMRI task representations of the neuropsychological test battery to measure cognition across eight domains: motor, visuospatial, attention, working memory, language and cognitive fluency, memory, affective processing, decision making and reward processing, and executive function. To date, 48 participants [mean (sd) age = 32(10) years; 28 female; 18 self-reporting as African-American, 28 Caucasian, 1 Hispanic, and 1 biracial] consented to participate in the study and met inclusion and exclusion criteria. All research procedures were conducted with oversight by the UAMS IRB. Participants underwent structured clinical interview (SCID-NP), two MRI sessions (1 h each), a battery of computerized assessments (1 h), and comprehensive neuropsychological assessment (2–4 h). Functional MRI data were acquired with standard parameters: TR/TE/FA = 2000ms/30ms/90, FOV = 240x240 mm, matrix = 80x80, 37 slices of 2.5 mm thickness with 0.5 mm gap, final resolution 3x3x3 mm3. Following data preprocessing (7), independent component analysis (8) identified functional brain networks previously reported in the literature (9). Task-based deconvolution via general linear modeling was used to assess functional activity of these networks across the 11 different Cognitive Connectome tasks. Finally, robust linear regression was used to relate the extent of networks' task-based activation to individual differences in cognition and behavioral performance. We report findings for the Judgment of Line Orientation task, which has the closest in-scanner replication of a neuropsychological test.
Results: Task-induced network activity varied markedly across participants, with visual networks showing the greatest consistency in activity [$t(37) > 6.4$, $p < 0.0001$] and frontal networks showing the greatest variability [$t(37) = -0.27$, $p = 0.81$]. Furthermore, accuracy of visuospatial judgment correlated with task-induced activation of the dorsal visual network [$t(37) = -3.04$, $p < 0.005$] but not primary visual network [$t(37) = -1.92$, $p = 0.064$] or ventral visual network [$t(37) = -1.34$, $p = 0.19$].
Conclusions: We have shown that canonical brain networks are recruited during task performance, and that the degree of network recruitment may reflect individual differences in cognitive ability. These results validate the Cognitive Connectome as a methodological framework for evaluating the neural encoding of cognitive variance. Understanding these brain-behavior relationships could critically enhance clinical decision making, particularly for patient selection (such as predicting cognitive decline following neurosurgery, or predicting the treatment to which a patient would optimally respond). The Cognitive Connectome's comprehensive exploration of neurocognitive variance offers an unprecedented approach for translating functional MRI into patient care.
Keywords: neuroimaging, neuropsychology, fMRI, cognition, individual differences
Disclosures: G. James, Nothing to Disclose; J. Fausett, Nothing to Disclose; J. Gess, Nothing to Disclose; T. Kearney-Ramos, Nothing to Disclose; C. Kilts, Nothing to Disclose.

M127. Low Fractional Anisotropy of the Right Ventral Anterior Cingulate Related to Depressive Symptoms in Atherosclerotic Vascular Disease

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Background: Patients with cardiovascular disease face elevated risk for depressive symptoms, and those who develop these symptoms are more likely to have poor long-term cardiac outcomes. The current study sought to characterize the relationship between the health of brain white matter and depressive symptoms in older adults with atherosclerotic vascular disease (AVD), a common form of cardiovascular disease. To measure white matter integrity, the current study used diffusion tensor imaging, a sensitive

measure which has not yet been widely utilized in participants with AVD. The study focused on the white matter underlying the ventral anterior cingulate cortex (vACC), given its strong relationship with depressive symptoms in other studies. The region of interest included the white matter underlying ventral Brodmann Area 24 as well as Brodmann Area 25, which are often termed subcallosal and subgenual cingulate, respectively.
Methods: Participants (N = 35) were 55—90 years old and all had a current unequivocal diagnosis of AVD and one or more of the following: history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, placement of coronary artery stent, or peripheral vascular disease. Those with dementia and/or history of stroke were excluded. Fractional anisotropy (FA) was used as an index of white matter integrity and organization. Mean FA was measured within the vACC via the standardized and automated application of the region of interest to each participant's brain scan. Depressive symptoms were measured using the Symptom Checklist-90-Revised (SCL-90-R) Depression Scale.
Results: Depressive symptoms were significantly related to low FA in the right vACC ($r = -0.361$, DF = 31, $p = 0.039$), but not the left vACC ($r = 0.259$, DF = 31, $p = 0.145$). The correlation coefficients were found to be significantly different between left and right vACC ($Z = 2.310$, $p = 0.012$), suggesting a critical role for the right, but not the left vACC in the pathophysiology of depressive symptoms in the current sample.
Conclusions: Poor white matter health in the right vACC may be a biological mechanism for depressive symptoms. Findings from various methodologies support the hypothesized critical role of the right hemisphere in the manifestation of depressive symptoms, especially in older adults and those with vascular disease. For example, the right hemisphere has shown an active role in the voluntary suppression of sadness, suggesting this may be a mechanism by which damage to the right hemisphere impairs emotional regulation. We suggest that, with additional research, the findings from the current study could be used to develop better treatments for older adults with vascular disease and depressive symptoms. For example, aggressive treatment of risk factors for vascular disease during middle age could significantly reduce the number of participants developing depressive symptoms in later life. Conversely, it is possible that neurosurgical interventions for treatment-resistant depression such as deep brain stimulation may be more effective when targeted to the right hemisphere in older adults with vascular disease. Targeting this region for antidepressant treatment may produce significant improvement in quality of life, medical morbidity, and mortality.
Keywords: Diffusion Tensor Imaging, Depression, Vascular Disease, Subgenual Cingulate, Subcallosal Cingulate
Disclosures: K. Rowe Bijanki, Nothing to Disclose; J. Matsui, Nothing to Disclose; H. Mayberg, Nothing to Disclose; V. Magnotta, Nothing to Disclose; S. Arndt, Nothing to Disclose; H. Johnson, Nothing to Disclose; P. Nopoulos, Nothing to Disclose; S. Paradiso, Nothing to Disclose; L. McCormick, Nothing to Disclose; J. Fiedorowicz, Nothing to Disclose; E. Epping, Nothing to Disclose; D. Moser, Nothing to Disclose.

M128. Moderate and Heavy Marijuana Use: Differences in Whole-brain Functional Network Structure That Underlie Iowa Gambling Task Performance

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Background: In recent years, both medicinal and recreational use of marijuana has increased while the perception that its use is harmful has decreased. As overall use becomes more prevalent, there is a growing need to thoroughly understand the consequences of marijuana exposure on important everyday behaviors, like decision-making. The Iowa Gambling Task (IGT) was the first neuropsychological task used to model real-life decisions in a way that factors reward, punishment, and uncertainty. Long-term heavy marijuana (HMJ) users have been shown to have deficits in IGT performance, and these deficits have been associated with changes in neural activity within the ventromedial prefrontal cortex (VMPFC). Understanding functional brain networks that underlie IGT performance may help elucidate relationships important to making decisions under ambiguous circumstances and that are disrupted after long-term heavy marijuana use. Therefore, the first goal is to evaluate these networks using graph theory methods. The second goal is to assess the effects of more moderate marijuana (MMJ) use on IGT performance and brain networks.
Methods: Behavioral and functional brain network data were collected from non-marijuana smoking Controls (n = 9; mean age ± SE: 24.3 ± 1.0 years old; age range: 21—30 years old), MMJ (n = 11; mean age ± SE: 23.0 ± 0.8 years old; age range: 21—30 years old) and HMJ (n = 11; mean age ± SE: 25.2 ± 0.8 years old; age range: 21—30 years old) users. MMJ users were defined as individuals that smoked no more than 15 out of 30 days in a month, and HMJ users were defined as individuals that smoked approximately every day. Behavioral performance at the beginning and at the end of the task was evaluated using Net Score, which was defined as the difference between advantageous and disadvantageous selections. Using a graph theoretic approach, voxel-wise functional brain networks were generated throughout performance at the beginning and the end of the task. Hubs were defined as brain regions that showed disproportionately high functional connectivity relative to the rest of the brain and group consistency maps were used to identify the location of hubs across groups.
Results: In the beginning stages of the task, all three groups performed poorly by predominately making disadvantageous selections (Mean Net Score ± SE: Control = −5.89 ± 3.85; MMJ = −3.83 ± 2.61; HMJ = −7.25 ± 1.19). Despite each group performing poorly, the Control and user groups showed distinct differences in the presence and location of hubs. In particular, the anterior insula served as a hub for both MMJ and HMJ users but not for Controls, who showed no presence of hubs. In later phases of the task, Controls and MMJ users predominately shifted to more advantageous selections whereas HMJ users did not improve (Mean Net Score ± SE: Control = 10.67 ± 5.86; MMJ = 7.75 ± 6.21; HMJ = -13.83 ± 2.41). Successful performance in Controls and MMJ users was accompanied by

distinct differences in hub location despite both groups outperforming HMJ users. Specifically, the VMPFC served as a hub in Controls whereas the anterior insula continued to serve as a hub in MMJ users but not HMJ users.
Conclusions: We show that marijuana user groups exhibit different functional brain networks compared to Controls despite equivalent poor performance at the beginning of the IGT. We also show that later in the task specific transitions in VMPFC hub structure underlie the ability to develop a successful strategy in Controls but not HMJ users. In addition, these data show that increased functional connectivity in the insular cortex throughout task performance may help maintain control-level performance in MMJ users. Future work will explore the relationship between functional network structure within the insular cortex and successful performance on tasks that model the decision-making process.
Keywords: Marijuana Use, Iowa Gambling Task, fMRI, Human Brain Functional Networks, Graph Theory
Disclosures: M. Moussa, Nothing to Disclose; L. Porrino, Nothing to Disclose.

M129. Executive Control Network Dysfunction in Major Depressive Disorder Patients with Early Life Stress: Preliminary Findings from the International Study to Predict Optimized Treatment in Depression

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Background: Early life stress (ELS), particularly when related to dysfunction within the family (e.g. physical and sexual abuse), is associated with increased risk for developing major depressive disorder (MDD) and more severe MDD course. Emerging findings demonstrate impaired cognitive control in individuals exposed to ELS, in a pattern similar to that found in MDD patients. These data highlight cognitive control as a core deficit common to ELS and MDD, and thus a potential mechanism by which ELS may confer vulnerability to poorer outcomes in MDD. We assessed behavioral and neural measures of cognitive control in relation to ELS history in MDD patients participating in the International Study to Predict Optimized Treatment in Depression (iSPOT-D), hypothesizing patients with ELS would exhibit greater impairments in executive control network functioning, and that such deficits would map to clinical outcomes.
Methods: 98 patients enrolled in iSPOT-D with baseline ELS, neurocognitive, and fMRI data were included in this analysis. iSPOT-D included patients 18–65 years old meeting DSM-IV criteria for non-psychotic MDD, randomized to 8-week open antidepressant treatment, with clinical response defined as 50% reduction in pre- to post-treatment Hamilton Depression Rating Scale (HDRS) score. The Early Life Stress Questionnaire, a 19-item self-report instrument, assessed ELS exposure prior to age 18 years. In this study ELS was defined categorically as presence versus absence of childhood physical and/or sexual abuse. Computerized cognitive testing with IntegNeuro software yielded summary performance scores across multiple cognitive domains such as attention, verbal and working memory, executive function, cognitive flexibility, and response inhibition. fMRI cognitive tasks included Oddball, Continuous Performance Task (CPT), and Go/No-Go. fMRI data were preprocessed with FSL with general linear models estimated in SPM8. A priori independently defined regions of interest within the executive control network were used to extract and analyze activation data. Repeated measures analysis of variance was used to assess neural modulation across task conditions, stratified by group.
Results: 24.5% of patients reported ELS (21.4% reported childhood physical abuse, 12.2% reported childhood sexual abuse). Patients with compared to without ELS were less educated, less often single/more often divorced, but were otherwise demographically similar. On neurocognitive testing, patients with compared to without ELS performed worse on tasks of attention and working memory (1-back CPT, forward digit span). On fMRI Oddball task, patients with compared to without ELS significantly differed in their dynamic modulation of left and right mid-dorsolateral prefrontal cortex (DLPFC), left anterior DLPFC, and left and right posterior DLPFC, with ELS patients failing to increase activation of these regions in response to increased attentional load (target versus non-target condition). In CPT, patients with compared to without ELS significantly differed in modulation of right mid-DLPFC, right posterior DLPFC, and left inferior parietal lobule, in response to changing task conditions/cognitive load (target versus non-target versus baseline conditions). HDRS response was predicted by increased right mid-DLPFC activation on the CPT task (baseline versus non-target condition), particularly in patients with ELS (significant right mid-DLPFC x group interaction; no main effect of ELS).
Conclusions: Among MDD patients, history of ELS conferred greater behavioral deficits in attention and working memory, and impaired dynamic modulation of executive control network regions in response to changing cognitive task demands. Moreover, our finding that differential right DLPFC modulation in response to CPT task load may mediate the relationship between ELS and treatment outcome, although preliminary, supports executive control network dysfunction as a potential neurobiological mechanism for adverse clinical outcomes associated with ELS.
Keywords: major depressive disorder, early life stress, neuroimaging, cognition, executive control network
Disclosures: S. Miller, Nothing to Disclose; L. McTeague, Nothing to Disclose; A. Gyurak, Nothing to Disclose; B. Patenaude, Nothing to Disclose; L. Williams, **Part 1:** Consultant, Brain Resource, **Part 2:** Consultant, Brain Resource, **Part 4:** iSPOT-D sponsor, Brain Resource ; A. Etkin, **Part 4:** iSPOT-D sponsor, Brain Resource ,

M130. Striatal Dopamine Transporter Availability in Obsessive-compulsive Disorder: A Randomized Clinical Trial Using [Tc99 m]-TRODAT-1 SPECT

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Background: Molecular brain imaging studies have provided evidence for a possible involvement of the dopaminergic system in the pathophysiology of obsessive-compulsive disorder (OCD). However, no prior study evaluated changes in the functional anatomy of this neurotransmitter in OCD patients before and after different treatments. Herein, we assessed pre-synaptic striatum dopamine transporters (DAT) density in treatment-naïve adults with OCD before and after either fluoxetine or cognitive-behavior therapy (CBT), and in a group of healthy controls.
Methods: OCD patients (mean age ± standard deviation: 30.6 years ± 11.3) and age matched-healthy controls underwent a [99 m]Tc-TRODAT-1 and single photon emission computerized tomography (SPECT) scan at baseline. Patients were then randomized to receive either fluoxetine (up to 80 mg/day) or group CBT for 12 weeks. Post-treatment TRODAT-1 scans were also conducted in 29 patients (14 in the fluoxetine-treated group and 15 in CBT-treated group). SPECT images were coregistered with structural magnetic resonance imaging (MRI). DAT density was calculated using the following formula: specific DAT binding in the region of interest - non-specific DAT binding in the cerebellum/non-specific DAT binding in the cerebellum. Right and left striatum DAT density between groups (patients and controls) were carried out using Mann–Whitney U-test, whereas Wilcoxon signed-ranks test was used to compare patients with OCD before and after treatment with fluoxetine and CBT.
Results: At baseline, OCD patients ($n = 41$) presented significant differences in DAT density compared to healthy controls ($n = 32$) in the right anterior putamen (mean DAT density ± standard deviation: 2.05 ± 0.36 for patients and 2.24 ± 0.37 for controls; $p = 0.031$) and a statistical tendency in the left anterior putamen (mean DAT density ± standard deviation: 2.04 ± 0.40 for patients and 2.27 ± 0.55 for controls; $p = 0.071$). Patients had lower binding ratios than healthy subjects. Twenty-eight subjects (14 fluoxetine-treated and 15 CBT-treated patients) completed the full 12-week treatment protocol. As a group, patients exhibited a significant reduction in the OCD symptom severity as measured by the Y-BOCS (reduction of 35%, $p < 0.001$). Individually, the fluoxetine and CBT subgroups displayed significant OCD symptom improvement (reduction of 39%, $p = 0.003$ and 33%, $p = 0.001$ respectively). There were no statistically significant changes in within-group analysis comparing DAT-BP before and after treatment when considering the entire group ($n = 28$) or CBT-treated patients ($n = 14$) in any of the regions investigated. Pre versus post-treatment analysis for fluoxetine-treated patients ($n = 14$) showed a statistical tendency of increment in DAT density in left caudate (increase of 11%, $p = 0.064$), left anterior putamen (increase of 11%, $p = 0.084$) and right anterior putamen (increase of 13%, $p = 0.095$). No statistically significant changes were observed in DAT density in patients submitted to CBT.
Conclusions: This study investigated the functional anatomy of dopaminergic system in a relatively large sample of treatment-naïve adult patients with OCD submitted to a randomized controlled clinical trial. Our results provides evidence for an involvement of the dopaminergic system in the pathophysiology of OCD, but do not support the involvement of DAT changes in the improvement of obsessive-compulsive symptoms. On the other hand, our findings do not rule out the possibility of dopaminergic changes at the post-synaptic level.
Keywords: Obsessive-compulsive disorder, dopamine transporter, SPECT, clinical trial, TRODAT-1
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M131. Cortico-amygdala Coupling as a Marker of Early Relapse Risk in Cocaine-addicted Individuals

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Background: Addiction to cocaine is a chronic, relapsing condition characterized by poor treatment retention, and high rates of early relapse. The present study builds on efforts to identify neural markers of relapse risk by employing resting state functional connectivity (rsFC) to interrogate neural circuits arising from the amygdala; a brain region implicated in multiple relapse-related processes including craving, anxiety and reactivity to stress following both acute and protracted withdrawal from cocaine and other drugs of abuse. To approximate relapse-related amygdala-circuitry identified within preclinical models, the current study divided the amygdala into basolateral (BLA) and corticomedial (CMA) divisions. It was expected that early relapse following treatment for cocaine addiction would be associated with enhanced rsFC between the BLA and dorsomedial prefrontal/dorsal anterior cingulate cortex (dmPFC/dACC), a circuit found to facilitate reinstatement of cocaine-seeking. Conversely, based on evidence linking ventromedial prefrontal/rostral anterior cingulate cortex (vmPFC/rACC) to down regulation of CMA output and inhibition of cocaine-seeking and negative affect, we expected reduced rsFC between the CMA and vmPFC/rACC to confer greater risk of relapse. Amygdala circuitry at the whole-brain level was also explored to identify novel circuits that may arise as a function of relapse risk.
Methods: Whole-brain resting-state fMRI connectivity (6 min) was assessed in 45 cocaine-addicted individuals (39 males) and 22 healthy controls (14 males). Cocaine-addicted individuals completed scans in the final week of a 2–4 week treatment episode (Minnesota Model). Bilateral BLA and CMA seed volumes were first generated as probabilistic volumes using FSL's Juelich Histological Atlas. Individual amygdala volumes (FreeSurfer volumetric segmentation) were then used to restrict probabilistic BLA and CMA seed voxels to the amygdala. Resting fMRI data were preprocessed and analyzed using AFNI. Within a week of their scan session, participants completed neurocognitive, and clinical measures, including the Iowa Gambling Task, Wisconsin Card Sorting Test, Trail Making Task Continuous Performance Task, Cocaine Craving Questionnaire, Obsessive Compulsive Cocaine Use scale. Trait stress reactivity was measured with the TCI Harm Avoidance

and NEO Neuroticism scales. Early relapse was considered any cocaine or psychostimulant use within the first 30 days post-treatment.
Results: As expected, relative to controls and non-relapse participants ($n = 21$), relapse within the first 30-days post-treatment ($n = 24$) was associated with reduced rsFC between the left CMA and vmPFC/rACC. No relapse-related effects were seen for connectivity between the BLA and dmPFC/dACC. Instead, a robust reduction rsFC between the bilateral BLA and visual processing regions (lingual gyrus/cuneus) was seen in non-relapse individuals compared to both controls and relapse participants. In cocaine-addicted individuals, reduced rsFC between the CMA and vmPFC was associated with greater perseverative responding on the Wisconsin Card Sorting Task. Cross validation analysis demonstrated that together CMA-vmPFC and BLA-lingual gyrus/cuneus connectivity can predict early relapse status with a 77% accuracy. In contrast, relapse was unrelated to measures of trait stress reactivity, executive control or clinical characteristics such as years of use, treatment duration, craving or obsessive compulsive cocaine use.
Conclusions: Reduced rsFC between the CMA and vmPFC/rACC among cocaine-addicted individuals at risk of early relapse may reflect a diminished capacity to down-regulate withdrawal-induced craving and reactivity to stress/anxiety known to be mediated by the CMA. The CMA is also implicated in stress-induced relapse to cocaine seeking. In contrast, the BLA has been implicated in the consolidation and reconsolidation of cocaine-associated cues and contexts that drive relapse to cocaine-seeking. The BLA receives extensive input from visual processing regions, but also projects back to the visual processing regions, a mechanism thought to underlie bottom-up regulation of sensory processing. Reduced rsFC between the BLA and visual processing regions in non-relapse individuals may reflect early bottom-up regulation of drug cues and stressful environmental stimuli which could otherwise precipitate early relapse in cocaine-addicted individuals. A similar mechanism has been implicated in treatment success for specific phobia. In sum, the current findings suggest that probing functional connectivity within neural circuits implicated in preclinical models of relapse to cocaine-seeking may provide a promising tool for assessing relapse risk in human cocaine-addicted individuals. Future efforts to replicate the current findings and alter connectivity within these circuits may also yield novel interventions and improve treatment outcomes.
Keywords: cocaine addiction, amygdala, connectivity, relapse
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M132. Distinct Types of Sensory Prediction-Error Signals in Schizophrenia with Active Psychosis

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Background: The pathophysiological mechanisms of psychosis in schizophrenia remain unclear. Prior work with functional magnetic resonance imaging (fMRI) in humans suggests that a disruption in prediction-error signals, discrepancy signals between expected and actual outcomes, may underlie psychotic symptoms in schizophrenia. However, work in non-human primates suggests at least two functionally distinct types of prediction-error signals (i.e., signed and unsigned prediction errors, which represent predictability and direction of the error or only predictability, respectively) that are encoded by segregated populations of dopamine neurons in the midbrain. Because these distinct prediction error signals are likely conveyed through different neural pathways and may have different roles in motivated behavior, their study in schizophrenia may provide important insights into the specific functional phenotype that ultimately gives rise to psychotic symptoms. Here, we used an auditory paradigm to study signed and unsigned prediction errors in patients with schizophrenia who had active psychotic symptoms and a group of healthy controls.
Methods: We recruited 10 participants with schizophrenia and a group of 10 matched controls. We used a sparse-sampling fMRI paradigm that consisted of the presentation of auditory and blank stimuli, varying the level of predictability of stimulus occurrence. Following each stimulus presentation, participants were asked to indicate via button press whether speech was present on that trial or not. Applying a predictive-coding algorithm, we computed trial-by-trial estimates of prediction errors for each trial type (stimulus trials and blank trials) and regressed these estimates against BOLD signals in each participant. Group-level analyses in SPM8 consisted of a group-by-trial-type ANOVA for between-group differences in prediction-error effects and region-of-interest-based Pearson correlation analyses.
Results: Across participants, we found an anatomical dissociation in the neural representation of signed and unsigned prediction errors: while signed prediction errors were encoded in the auditory cortex, unsigned prediction errors were encoded in the midbrain, ventral striatum, thalamus, and dorsal anterior cingulate (all $p < 0.05$, corrected). Signed prediction errors in the auditory cortex were significantly weaker in patients than in controls as were unsigned prediction error signals in the dorsal anterior cingulate ($p < 0.05$, corrected). In addition, post-hoc ROI analyses showed that patients had weaker unsigned prediction error signals in the midbrain and thalamus.
Conclusions: Consistent with prior work, our results suggest an anatomical dissociation in the neural representation of signed and unsigned prediction errors in humans that further extends to the sensory domain. While this dissociation is preserved in patients with schizophrenia, the magnitude of signed prediction errors in the auditory cortex and of unsigned prediction errors in subcortical regions and the dorsal anterior cingulate is diminished in patients relative to controls. These findings thus suggest that an abnormality in both signed and unsigned prediction errors could contribute to psychosis in schizophrenia although further research into the clinical and neuropsychological correlates of these dissociable signals is warranted.
Keywords: model-based fMRI; sensory learning; prediction error; schizohrenia; psychosis

Disclosures: G. Horga, Nothing to Disclose; A. Abi-Dargham, Nothing to Disclose; B. Peterson, Nothing to Disclose.

M133. Poor Amygdalofrontal Connectivity Predicts Symptomatic Deterioration in At-risk Youth

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Background: Young adults with mild, subsyndromal symptoms of depression or psychosis are at elevated risk for developing more serious psychopathology later. However, the presence of these mild symptoms alone has poor predictive power—the majority of these subsyndromal states are transient and do not worsen or become sustained over time. Thus, better methods for determining whether the presence of mild symptoms in a young person is associated with actual risk for psychopathology are greatly needed. Such advances would permit the monitoring or initiation of preventive interventions in those at imminent risk. Prior work has supported the hypothesis that abnormalities in neural circuitry involved in generating emotion and social behavior, most prominently the amygdala and medial prefrontal cortex (mPFC), are associated with risk for mood and psychotic disorders. Moreover, evidence for changes in the connections within these networks in patients with these disorders has suggested that subtle changes in connectivity may precede regional brain abnormalities and illness onset. Therefore, in the current study we tested the hypothesis that amygdala-mPFC functional connectivity (measured using resting-state functional MRI) is weaker in at-risk young people who will worsen over time, compared to those who do not.

Methods: Young adults who were attending two Boston area universities participated in an in-person campus screening for symptoms of depression and psychosis, which involved filling out a set of standard questionnaires, and a brief clinical interview for those who were deemed at risk. Subjects were considered to be at some risk for sustained/worsening psychopathology if one of three criteria were met: having a score on the Beck Depression Inventory (BDI), a measure of symptoms of depression, > 5; a score on the Peters *et al* Delusions Inventory (PDI), a measure of delusional thinking and other unusual experiences, which has been validated for use in the general population, > 7; a score on the suicide item of the BDI > 0. Those found to be at-risk, plus a small number of healthy controls and clinically depressed subjects, were then asked to participate in: 1) one MRI (3 T Siemens TIM Trio scanner) scanning session, which included a resting-state blood oxygenation level dependent (BOLD) scan, and 2) longitudinal follow-up assessments of symptoms conducted via on-line self-report questionnaires. To test our hypothesis, a seed-based functional connectivity analysis was conducted using the resting-state BOLD data. An independently defined, atlas-based amygdala seed and a mPFC (BA10) seed (derived from an independent dataset collected in a healthy cohort described in Andrews-Hanna *et al*, 2010) were used. Pearson's coefficients representing correlations in low frequency fluctuations ($<$ .08 Hz) in the BOLD signal between these two regions were extracted and z-transformed. Then correlations were computed between these amygdala-mPFC connectivity values and 1) change in depression (BDI score) and 2) change in psychotic symptoms (PDI score) from baseline to the one year follow-up time point. In addition, voxel-wise, whole brain regression functional connectivity analyses using the amygdala seed, and the individuals' change scores (BDI or PDI) as a regressor, were also conducted (whole brain corrected, False Discovery Rate $p < 0.05$).

Results: One year follow-up data and MRI scans of sufficient quality were available for 28 subjects. Baseline amygdala-mPFC connectivity was found to be negatively correlated with change in PDI score ($r = -0.51$, $p = 0.006$), i.e., subjects with weaker amygdala-mPFC connectivity showed increases in psychotic symptoms at one year. There were no correlations between amygdala-mPFC connectivity (as measured using the predefined seeds) and change in BDI score. The whole brain voxel-wise regression analyses confirmed that there was a strong association between poor amygdala-mPFC (BA10) connectivity and subsequent increases in psychotic symptoms, and revealed a significant association between poor amygdala-mPFC (BA9) connectivity and increases in depression.

Conclusions: These data suggest that low amygdala-mPFC connectivity may represent a marker of vulnerability in young adults, indicating that they are at risk for subsequent symptomatic worsening. Replication in other cohorts will be needed to determine the true predictive value of this measure. If confirmed, these findings suggest that impaired communication between frontal and subcortical limbic areas represent one of several indicators of incipient illness and ultimately may serve as a fruitful intermediate target for trials of preventive interventions.

Keywords: amygdalofrontal, functional connectivity, longitudinal, psychosis, depression

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M134. Ketamine-induced Changes in [11C]ABP688 Binding in Healthy Human Subjects

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Background: The purpose of this study was to evaluate the effects of ketamine upon the binding of [^{11}]ABP688, a negative allosteric modulator of mGluR5 receptors. Ketamine is an NMDA glutamate receptor antagonist with anesthetic and analgesic properties that has been studied as a probe of NMDA receptor dysregulation in psychiatric disorders. Most recently, it has received intensive study in light of its rapidly emerging antidepressant effects. This study was intended to test the hypothesis that ketamine, through its ability to stimulate glutamate release, would thereby alter the affinity of [^{11}C]ABP688 for the mGluR5 receptor. If this effect of ketamine could be demonstrated, it might suggest that this paradigm might be developed as an indirect non-invasive assay for glutamate release.
In this way, this method might inform the study of the antidepressant effects of ketamine and glutamatergic dysregulation in psychiatric disorders.
Methods: Ten healthy nonsmokers (33.5 ± 13.2 years) participated in two [^{11}C]ABP688 PET scans on the same day—one before (scan 1) and one during i.v. ketamine administration. Ketamine was administered as follows: 0.23 mg/kg over 1 min, then 0.58 mg/kg over 1 h. [^{11}C]ABP688 was injected as a bolus (576.2 ± 135.6 MBq for scan 1; 593.4 ± 115.8 MBq for scan 2) and PET emission data were acquired for 90 min. Input functions were obtained through arterial blood sampling with metabolite analysis. Time-activity curves (TACs) were generated and an unconstrained two-tissue compartment model was used to fit TACs and estimate distribution volume, V_T. Subjects were assessed for mood and cognitive functioning at baseline, immediately after ketamine administration, and 24 h after ketamine administration.
Results: We observed a reduction in [^{11}C]ABP688 V_T at scan 2 in all brain regions assessed (such as the anterior cingulate 19.2%, amygdala 26.7%, dorsolateral cortex 18.2%, hippocampus 21.2%, medial frontal cortex 19.5%, and thalamus 20.3%). There was a statistically significant impairment in memory immediately post ketamine dose, which resolved by the 24 h assessment. Conversely, no impairments were observed immediately post ketamine on measures of executive function.
Conclusions: We show that [^{11}C]ABP688 binding is vulnerable to ketamine-induced changes in brain neurochemistry. Caveats include the fact that [^{11}C]ABP688 binds to an allosteric modulator site on mGluR5 (and not the glutamatergic site), thus change in binding is likely not due to direct competition with glutamate, but probably due to

modulations of the receptor function as a result of increases in glutamate. Although, further examination is required to understand the individual variation in ketamine response, this paradigm can be applied to study effects of ketamine in diseased brain and further our understanding of its mechanism of action. This can rapidly and effectively aid in the development of novel antidepressants that target the glutamatergic system.

Keywords: mGluR5, [11C]ABP688, ketamine, depression, glutamate

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M135. Modafinil-induced Enhancement of Learning and Related fMRI Activation in Humans Reflects Individual Differences in Striatal Dopamine D2/D3 Receptor Availability

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Background: Modafinil is an analeptic medication that has been shown to enhance cognitive function in patient populations with difficulties, such as those with ADHD, schizophrenia, and addictions. As part of a complex mechanism of action, modafinil inhibits the dopamine transporter, thereby modulating intrasynaptic dopamine, which has a role in facilitating learning. We have reported that modafinil is especially effective in enhancing cognition and neural activity in individuals with low learning performance at baseline (Ghahremani *et al*, 2010), suggesting that underlying individual differences in baseline neurotransmission can influence the response to modafinil. In addition, methamphetamine-dependent (MA) individuals, which as a group had lower associative learning performance than healthy control (HC) participants, showed greater modafinil-induced improvement in performance and greater related brain activation. Given consistent reports of individual differences in the impact of modafinil on cognitive performance (meta-analysis, Repenti *et al*, 2009) and the view that hypo-dopaminergic function in MA may underlie low performance by this group, we hypothesized that variation in baseline dopaminergic function can substantially influence the response to modafinil. Therefore, we tested whether a marker for dopamine signalling (specifically D2-type receptor availability, D2R) was related to the magnitude of modafinil-induced changes in learning performance and related brain activation in both MA and HC groups. We specifically hypothesized that individuals with lowest striatal D2R would show the largest improvement in learning and greatest increase in task-related activation in the striatum.

Methods: We assessed the relationship between baseline measures (without medication) of dopamine D_2/D_3 receptor availability (using [F-18]fallypride positron emission tomography) and functional MRI of associative learning in a randomized, double-blind, placebo-controlled study with 27 participants. Modafinil (200 mg) and placebo were administered orally, in counterbalanced fashion, 2 h before each of two fMRI sessions. We hypothesized that individuals with low striatal receptor availability would show the largest improvement in learning and greater related activation in the striatum.

Results: Across groups (controlling for group, age, and sex),receptor availability was negatively correlated with the magnitude of modafinil effects on both learning performance and task-related striatal fMRI activation; individuals with lower receptor availability showed a bigger improvement in performance and greater activation during modafinil versus placebo conditions. The change in performance was positively related to the change in striatal fMRI activation. When the individual groups were considered separately, no significant correlations were observed between striatal D2R and modafinil effects on learning. This may reflect the reduced power in the smaller individual groups compared with the larger combined sample as well as a small dynamic range in striatal D2R among the MA subjects.

Conclusions: These results suggest that striatal function has an important role in mediating the effects of modafinil on learning, and that variation in cognitive enhancement across individuals is, in part, determined by striatal dopaminergic function. This is an example of how selection of pharmacotherapy options can be improved by personalization of treatment through consideration of individual differences.

Keywords: dopamine, fMRI, PET, modafinil, learning

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M136. Social Impairment Is Related to Frontolimbic Structural Connectivity and Functional Activity in Autism Spectrum Disorders

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Background: Autism spectrum disorders (ASD) are characterized by impairments in social interaction and social communication, as well as repetitive interests and activities. Individuals with ASD exhibit varying degrees of symptomatology, supporting a dimensional approach to assessment in this population. Behavioral measures, such as the Social Responsiveness Scale (SRS), provide a quantitative measure of core symptom severity in ASD. Magnetic resonance imaging (MRI) studies to date have found evidence of decreased connectivity spanning brain regions implicated in social impairment in individuals with ASD. These regions, in part, are connected by the uncinate fasciculus (UF), an intrahemispheric tract connecting

medial temporal areas (e.g., amygdala) with frontal cortices. Here we investigated the relationship between SRS scores and structural connectivity in UF and functional activity during face processing in children and adolescents with ASD.

Methods: Sixteen individuals (mean age, 10.5 ± 2.5 y; range, 8–16 y; mean FSIQ, 83) with ASD received MRI scans. The scans were obtained at baseline as part of a pilot study of aripiprazole vs. placebo on brain activation in ASD. Eligibility for this study was determined by a Clinical Global Impressions-Severity (CGI-S) score of $\geqslant 4$ (moderately ill) and an Aberrant Behavior Checklist-Irritability (ABC-I) subscale score of $\geqslant 18$. All participants were psychotropic medication-free. Behavioral measures were obtained, including the SRS, a 65-item informant-based scale that measures several aspects of social relatedness. Higher scores on the SRS indicate greater impairment in social functioning. Scans were obtained on a 3 T Siemens Tim Trio scanner. After a high-resolution anatomical scan, participants performed a facial emotion processing task during fMRI and underwent diffusion tensor imaging (DTI). The fMRI task consisted of interleaved face and shape blocks. Each block consisted of six trials, with participants instructed to match (via button-press) one of two bottom images with a top target image: either the same emotional expression (angry or sad) for face blocks, or the elliptical image with the same orientation for shape blocks. The scan lasted three minutes, with four shape and three face blocks. The BOLD time series was acquired via a T2*-weighted echo-planar imaging (EPI) scan (39 slices; TR = 2250 ms; voxel size = 2.5x2.5x3.5 mm) and was preprocessed using AFNI software. Conditions were modeled by convolving a hemodynamic response function with the block-design time series, and face and shape regression coefficients were contrasted (face—shape). DTI images were obtained using a SE-EPI DTI sequence (matrix = 128x128; FOV = 256x256 mm; TE/TR = 77/8300 ms; 68 transverse slices; 2 mm thickness; 48 diffusion directions). DTI images were corrected for motion and eddy artifacts, and the FMRIB Diffusion Toolbox (FSL; FMRIB Center, Oxford) was used to calculate the FA map for each individual. Using tract-based spatial statistics (TBSS), FA maps were nonlinearly registered to the FMRIB58_FA template and affine-transformed into standard MNI space. Each participant's FA image was then projected onto a mean FA skeleton, resulting in individual skeletonized FA maps. An FA skeleton (thresholded at mean FA > 0.2) was then established. This mask was combined with the ICBM-DTI-81 parcellation map, and mean FA from left and right UF was calculated. Bivariate correlations were calculated between SRS scores and UF FA means. In addition, we examined the association of both SRS scores and UF FA with activity across the entire brain (voxel-level $p < 0.01$, $k > 110$ contiguous significant voxels to correct for multiple comparisons).

Results: Of the 16 participants scanned, one was removed from fMRI analysis due to excessive movement, and another did not undergo DTI. SRS scores ranged from 74–150 (mean, 115.6 ± 23.1). The BOLD response during the facial emotion processing task demonstrated a pattern consistent with emotional face viewing and higher-order cognition, with higher bilateral dorsolateral prefrontal cortex, amygdala and lateral occipital cortex responses to emotional faces compared to shapes. SRS scores were negatively associated with face—shape activity in two distinct clusters: fusiform gyrus (245 voxels) and anterior cingulate (143 voxels), indicating that poorer social functioning was related to lower face-related activity in these regions. In addition, left UF FA was associated with higher face-related activity in a large anterior cingulate cluster (359 voxels), though right UF did not demonstrate any significant relationships with brain activity. Finally, SRS scores were negatively correlated with left UF FA ($r = -0.66$, $p = 0.007$), with a similar trend for right UF FA ($r = -0.50$, $p = 0.056$).

Conclusions: This preliminary study investigated the neural correlates of social impairment in youth with ASD. Better social functioning in youth with ASD was associated with more mature frontolimbic white matter tracts and higher anterior cingulate and fusiform gyrus activity during an emotional face processing task. These findings support a relationship between the strength of long-range brain connections and core symptom severity in ASD. Large-scale studies are needed to confirm these preliminary results.

Keywords: Autism Spectrum Disorder, Diffusion Tensor Imaging, Functional Magnetic Resonance Imaging, Social Impairment

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M137. Watching Cerebral Blood Flow Using fMRI

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Background: Perfusion is one of the most important physiological and pathophysiological parameters in the brain, which has direct associations with central nerve system diseases, drug effects and therapeutical manipulations (Essig, Shiroishi *et al.* 2013). In the past few decades, several MRI methods have been developed to assess the perfusion parameters (i.e. cerebral blood flow, volume). They use either the exogenous contrast agent (i.e. gadolinium-based agent) (Cha, Knopp *et al.* 2002) or the endogenous contrast agent (i.e. labelled arterial blood water)(Chen, Wang *et al.* 2011). However, their impact in the field of psychopharmacology is limited due to its complexity, high cost, invasiveness (e.g. injection of the exogenous contrast agent) etc. Here we propose a novel data-driven method, which can track cerebral blood flow using an intrinsic oscillation in the fMRI data. The method can be applied to any fMRI data (shorter TR is preferable). In addition to the result from functional analyses, a dynamic map of cerebral blood flow would be generated simultaneously, which might help explain the functional result.

Methods: fMRI resting state studies were conducted in 7 healthy participants (4 females, 3 males; ages: 25 ~ 50). In resting state studies, participants were asked to lie quietly in the scanner and view a gray screen with a fixation point in the center. The resting state scans lasted 360 s or 600 s (for testing purposes). All MR data was acquired on a Siemens TIM Trio 3 T scanner (Siemens Medical Systems, Malvern, PA) using a 32-channel phased array head matrix coil. Multiband EPI (University of Minnesota sequence cmrr_mbep2d_bold R008) (Feinberg, Moeller *et al*. 2010) sequence was applied with TR = 400ms. To analyze the data, the procedure started with a seed voxel selected from the big blood vessels from fMRI data. The cross correlations were carried out between this blood oxygenation level dependent (BOLD) signal and all the other BOLD signals to select the voxels that have the highest correlation coefficient (> 0.5) at time lag 1 (or −1; the sign decides the direction in time of search). The sum of these selected BOLD signals formed a new regressor with time shift 1 (or −1), which will be used to replace the initial seed. Recursively, multiple self-evolving regressors with specific time shifts were generated until the number of selected voxels from the previous regressor became very small (i.e. below certain threshold). Then the regressors were used in the general linear model based analyses (Feat in FSL (Smith, Jenkinson *et al*. 2004)). The resulting z-statistics maps were concatenated to show dynamically the cerebral blood flow.
Results: 1) The dynamic changes in the result represent the cerebral blood flow in the brain; 2) The mean transit time automatically generated by the method was 4.6–7.2 s, which matched the previous findings (Crandell, Moinuddin *et al*. 1973). 3) The method has been proven to be very robust regardless of the selections of the seed.
Conclusions: To the best of our knowledge, this is the first study on tracking cerebral blood flow dynamically using self-evolving regressors generated from the BLOD fMRI data itself. Even though the method of using temporally shifted blood signal in low frequency to track cerebral blood flow was not new (Tong and Frederick 2010), there are two very profound findings in this study that might have huge impact on the fMRI data analyses, including understanding physiological signals, exploring drug effects on brain functions through blood circulation, etc. First, the blood-related systemic signals in fMRI are dynamic and evolve as they travel though the brain. Second, these signals can be extracted using recursive procedure, which is proven to be robust. We will apply this method on te population of cigarette smokers to assess the brain function and cerebral circulation associated with craving before and after smoking.
Keywords: fMRI, perfusion, cerebral blood circulation
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M138. Early Life Stress and Intra- and Extra-Amygdaloid Effective Connectivity

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Background: Chronic stress has been proposed to play a key role in the etiology of several affective and anxiety disorders vis-à-vis the influence of stress on amygdala structure and physiology (1, 2) . Specifically, the presence of early life stress (ELS) is linked to enhanced amygdala reactivity in both healthy controls (HC) and major depressive disorder (MDD) but is not observed in the absence of ELS among either HC or MDD (3, 4). Although the amygdala is typically regarded as a singular structure present in both hemispheres of the human brain, the human amygdaloid complex is actually comprised of thirteen heterogeneous nuclei and cortical regions (cf. Freese and Amaral, 2009). The most clearly defined functionally of these nuclei being the central nucleus (CeA; fear expression), lateral and basal (BLA; consolidation of fear learning) and superficial (SF; a relay system for learning based autonomic and output). Despite the differential and opposing pattern of amygdala reactivity among HCs based on the presence/absence of ELS history, it remains unclear which nuclei underlie these differences and whether intra- and extra-amygdaloid connectivity is affected.
Methods: Twenty one healthy controls with no history of Axis I disorders based on evaluation with the Structured Clinical Interview for DSM-IV (SCID) were administered the Childhood Trauma Questionnaire-Short Form (CTQ-SF) and scanned using functional magnetic resonance imaging (fMRI) during a conditioning paradigm investigating the predictability of stress (i.e., CS + ; CS + UCS; UCS). Groups were created based on CTQ-SF scores indicating presence/absence of ELS. After standard preprocessing, both beta weight values and the mean time series were extracted from nine regions of interest (ROIs) bilaterally including amygdala subregional nuclei based on probabilistic anatomical maps (5). The underlying neuronal response for these times series were extracted and the hemodynamic response deconvolved and input into a dynamic multivariate auto-regressive model (dMVAR) to obtain the connectivity matrices, which were then populated into different samples.
Results: Repeated measures ANOVA with group as the between subjects measure and trial type as the repeated measure found a main effect for response to the UCS for trial type (left; $p = 0.009$ and right; $p = 0.01$) and a non-significant trend for group x trial type (left; $p = 0.07$ and right; $p = 0.34$) and the main effect of group (left; $p = 0.31$ and right; $p = 0.15$). Follow up comparisons found robust differences between BLA and SF (left; $p = 0.005$ and right; $p = 0.01$), CeA and SF (left; $p < 0.05$ and right; $p = 0.01$) but not CeA and BLA (left; $p = 0.41$ and right; $p = 0.74$). Subsequent directional connectivity analysis of intra- and extra-amygdaloid connectivity demonstrated differential patterns. Specifically, ELS-exposed controls demonstrated a pattern of 'hyperconnectivity' originating temporally from right CeA for both intra- and extra-amygdaloid connectivity not observed in non-ELS related HCs.
Conclusions: While anatomical parcellation and intra-amygdaloid connectivity is well mapped in animal models, to our knowledge this is the first study to demonstrate a relationship between early life stress and amygdala sub-regional nuclei function in healthy humans with no history of psychiatric disorder. In particular, the absence of ELS appears to be associated with narrowly defined, function specific intra- and extra-amygdaloid connectivity consistent

with an inverse relationship between nuclei underlying fear learning and fear expression and moderate reactivity to aversive stimuli. In contrast, a history of ELS was associated with enhanced output from all amygdala subregional nuclei, as well as enhanced connectivity originating from CeA, consistent with robust intra- and extra-amygdaloid connectivity. Given the importance of CeA in fear expression, stress-related glucocorticoid output and autonomic arousal, this pattern may underlie significant risk for both medical and psychiatric illness.

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M139. Buspirone Blocks Dopamine D3 Receptors in the Non-human Primate Brain when Administered Orally

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Background: Converging lines of evidence indicate that dopamine D_3 receptor (D_3R) antagonists may be effective as treatments/medications for substance use disorders (SUDs) in animal and human. However, no selective D_3R antagonists are clinically available for testing this hypothesis. Buspirone (Buspar®) originally characterized as a selective 5-HT_{1A} partial agonist, has been used as an anxiolytic for more than 25 years. However, buspirone also binds to D_3R and D_4R with high affinity as an antagonist and with lower affinity to D_2R *in vitro*. Recently, this azapirone has been shown to interfere with cocaine reward in non-human primates. Here we evaluate buspirone's ability to block D_3R in the non-human primate brain and compared it to D_2R and D_1R blockade in pharmacologically-relevant and safe dose ranges.

Methods: In six female baboons, we used PET with [^{11}C]PHNO (D_3R-preferring radioligand), [^{11}C]raclopride (D_2R/D_3R radioligand) and [^{11}C]NNC-112 (D_1R radioligand) to measure occupancy of oral versus parenteral (IM) buspirone at multiple time points after drug administration. One of major metabolites, 6'-OH buspirone (IM, 1 mg/Kg) was also administered at 3 h before [^{11}C]PHNO scan.

Results: Intramuscular administration of buspirone (0.19 and 0.5 mg/Kg) showed high occupancy (50–85%) at 15 min and then rapid wash-out by 2 h in a dose dependent manner for both [^{11}C]PHNO and [^{11}C]raclopride PET studies. Interestingly, oral buspirone (3 mg/Kg) significantly blocked [^{11}C]PHNO binding in globus pallidus and substantia nigra (55–74% after 3 h), while blockade of [^{11}C]raclopride was minimal (10%) in striatum. One of buspirone's metabolites, 6'-OH buspirone (D_3R antagonist) significantly also blocked (89%) [^{11}C]PHNO binding in substantia nigra. No blockade was observed for [^{11}C]NNC-112 by both oral and parental administration of buspirone.

Conclusions: Since [^{11}C]PHNO binding has been known to reflect D_3R binding predominantly and little blockade was observed in [^{11}C]raclopride (D_2R/D_3R radioligand) binding after oral buspirone, we conclude that oral buspirone/its metabolites blocked D_3R significantly and would merit testing for therapeutic efficacy in SUDs in human.

Keywords: addiction, treatment, striatum, pallidum, buspirone, D3 receptors

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M140. A Novel fMRI Task to Evaluate Social Reward and Social Threat Hypersensitivity in Depressed Mothers of Psychiatrically Ill Children

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Background: Maternal depression constitutes an important risk factor for childhood psychiatric illness and poor child treatment outcomes. By contrast, when maternal depression is effectively treated, offspring have improved functioning as well. Response rates to conventional depression treatments are unsatisfactorily low, however, leaving large numbers of mothers and offspring at high risk for poor outcomes. Little is known about biologic mechanisms that may moderate or mediate mother-child dyadic outcomes, and yet better understanding of these processes may ultimately lead to interventions that could improve outcomes for this high risk population. We hypothesize that anomalies in neural processing of social threat and reward may play key roles in the biology of depression in mothers with psychiatrically ill offspring. For instance mothers might show altered response in neural regions relevant to processing negative stimuli (e.g., amygdala, insula), rewarding stimuli [(e.g., medial prefrontal cortex (mPFC)], social stimuli (e.g., mPFC, precuneus), and altered emotion

regulation (e.g., ventrolateral PFC). These neural patterns may, in turn, be associated with altered dyadic interactions such as emotional and physiologic reactivity to child-related stressors, diminished positive affect/warmth with their children, and maladaptive parenting style. The goal of this project was to develop novel fMRI tasks to evaluate depressed mothers' response to ecologically valid social reward and social threat, utilizing prompts from family-relevant interpersonal interactions with their psychiatrically ill children.

Methods: Mothers with a DSM-IV defined recent history of major depressive disorder ($n = 21$) and their children age 7–18 with a recent history of at least one internalizing disorder (one child/family) participated in this study. Data was collected on prior psychiatric history, current mood symptoms, and child-reported maternal warmth. Mothers-child dyads engaged in a family interaction session that was videotaped for use as fMRI stimuli. During the Event Planning Interaction task (positive affect/social reward), mother and child were asked to discuss activities that families may enjoy doing together (i.e., family holiday party, going on a vacation). During the Problem-Solving Interaction task (negative affect/social threat), mother and child were asked to discuss activities likely to engender 'mild to moderate' conflict for both (i.e., conflict with siblings, problems with homework). Mothers participated in fMRI scanning on a Siemens 3 T TIM Trio scanner. fMRI tasks incorporated as stimuli 20-s video segments of children from the family interaction session, determined to be positive, negative, or neutral based on reliable coders' ratings. Video segments of the participant's child or an unfamiliar child matched for gender and approximate age (i.e., unfamiliar child control) were presented in a block design, interspersed with 15-s fixation periods. Preprocessing and whole-brain analysis of fMRI data were completed using Statistical Parametric Mapping (SPM8) software. Predetermined condition effects at each voxel in whole-brain analyses were calculated in SPM as a t-statistic using multilevel models to account for nesting of time points and voxels within participants. All results survived family-wise error correction with $p < 0.05$ to control for multiple comparisons.

Results: Data collection yielded 18 usable scans. As predicted, during positive stimuli, mothers exhibited response to own child > unfamiliar child in the ventrolateral PFC (179 voxels, $t = 7.26$). During negative stimuli, mothers exhibited response to own child > unfamiliar child in the insula (e.g., 770 voxels, $t = 5.99$). Mothers' lifetime number of depressive episodes was related to less posterior cingulate (2064 voxels, $t = 5.30$) and precuneus (1302 voxels, $t = 5.08$) response to own positive > unfamiliar positive and more mPFC response to own negative > unfamiliar negative (553 voxels, $t = 5.32$). Child-reported level of maternal warmth was related to greater posterior cingulate and precuneus (1172 voxels, $t = 4.24$) response to own negative > unfamiliar negative.

Conclusions: This novel, ecologically valid task using stimuli of depressed mothers' own children appears to reliably engage brain regions associated with emotional, reward, and social processing. Given the salience of these stimuli, the implicit requirement to regulate emotion in response to them, and the affective difficulties experienced by mothers with major depressive disorder who parent a psychiatrically ill child, these findings indicate that the task is a valid way to elicit interpersonal responding (1) within the parent-child relationship and (2) in the context of maternal depression specifically. Mothers' responses were associated with clinical course (e.g., number of episodes) and to parenting-related warmth, suggesting its sensitivity to both clinical variables and family context. These novel tasks may be useful tools for exploring the neural basis of shared vulnerability to social and emotional difficulties across psychiatrically ill maternal-child dyads.

Keywords: maternal depression, social processing, reward, children

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M141. Disrupted Resting State Functional Connectivity in Unmedicated Patients with Schizophrenia

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Background: The hippocampus is one of the areas in the brain that is consistently implicated in the pathophysiology of schizophrenia. One promising technique to evaluate functional brain abnormalities is resting state functional MRI (fMRI), which allows investigation the synchrony of spontaneous neural activity between brain regions.

Methods: We conducted a resting state fMRI study in 22 unmedicated patients with schizophrenia (SZ) and 22 matched healthy controls (HC). Clinical assessments performed included the Brief Psychiatric Rating Scale (BPRS) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). All imaging was performed on a 3 T scanner. The resting state scan was acquired during a five-minute gradient recalled EPI sequence. Preprocessing included slice time correction and realignment, normalization to MNI space, smoothing using DARTEL. Nuisance regressors included the six motion parameters, and components of white matter and CSF explaining 90% of signal variance identified using a principal component analysis. Following data preprocessing and motion scrubbing, statistical parametric maps of the hippocampus were calculated for each participant by extracting the first principle component of the time series from a structurally defined mask of the left hippocampus (AAL atlas). The resulting volume of interest was regressed on whole brain BOLD signal to produce a functional connectivity map with every other voxel in the brain. Group-level functional connectivity maps were obtained by performing one-sample t-tests on each group's participant level functional connectivity maps. Group differences were assessed using a two-sample t-test on groups' participant level functional connectivity maps. All analyses were corrected for multiple comparisons at the cluster level using the false discovery rate, $p < 0.01$. In a post hoc

analysis, we explored correlations between hippocampus-precuneus (segmented into subregions based on Margulies *et al.* [1]) functional connectivity strength and clinical variables. To extract connectivity strength, eigenvariates were extracted from the hippocampus and all precuneus subregions, correlated and then z-transformed.
Results: HC and SZ did not differ in age, gender, parental occupation or smoking status. We found hippocampal resting state functional connectivity to the precuneus to be significantly decreased in SZ compared to HC [t(4.22), cluster extent (kE) = 751, $p_{FDRcor}r = 0.001$, MNI coordinates: x = −4, y = −56, z = 44]. We did not find correlations between hippocampus- precuneus connectivity strength (all subregions) and clinical variables (BPRS positive symptom scale, BPRS negative symptom scale, RBANS total score) (all $p > 0.05$).
Conclusions: Our results show resting state functional connectivity deficits between the hippocampus and precuneus in unmedicated patients with schizophrenia. While functional connectivity between these areas in working memory tasks has been related to performance in healthy subjects, we were unable to detect correlations between RBANS scores and functional connectivity strength. This could possibly be attributable to the lack of precision in measuring relevant domains using the RBANS. Further studies will need to be conducted to elucidate behavioral correlates of our findings. [1] Margulies, DS; *et al.* Precuneus shares intrinsic functional architecture in humans and monkeys. Proc Natl Acad Sci USA, 2009 106(47):2069–47
Keywords: Schizophrenia, hippocampus, resting-state, fMRI
Disclosures: N. Kraguljac, Nothing to Disclose; D. White, Nothing to Disclose; J. Hadley, Nothing to Disclose; A. Lahti, Nothing to Disclose.

M142. Connectivity Deficits in Chronic Stress and Depression: Resilience, Reversibility, and Clinical Implications

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Background: Chronic stress may precipitate episodes of depression in susceptible individuals, but the mechanisms are poorly understood. Stress causes atrophy of prefrontal dendritic arbors and loss of post-synaptic dendritic spines in rodent models and parallel deficits in prefrontal connectivity in healthy human subjects. Whether and how these deficits may contribute to the pathogenesis of depression is unknown. Here, we used resting state functional magnetic resonance imaging (rs-fMRI) to quantify functional coupling in two large-scale neuronal networks—the frontoparietal executive control network (ECN) and the medial prefrontal/medial parietal default mode network (DMN)—in chronically stressed, healthy human subjects and in actively depressed patients before and after a 5-week course of transcranial magnetic stimulation.
Methods: In Study 1, we used rs-fMRI to measure functional connectivity within and between the DMN and ECN in chronically stressed, healthy human subjects who were preparing for a major academic exam and in healthy unstressed controls. Subjects were categorized as exhibiting 'high resilience' or 'low resilience' based on their responses on the Cohen Perceived Stress Scale. To test for reversibility and control for confounds unrelated to stress, the same subjects were re-scanned in a second session, 4–6 weeks after cessation of the stressor. In both sessions, subjects were tested on an attention-shifting task that measured top-down executive control capabilities. In Study 2, we used rs-fMRI to measure functional connectivity in a cohort of patients with major depressive disorder, before and after a five-week course of transcranial magnetic stimulation (TMS) and in a closely matched cohort of healthy controls. Motivated by prior reports, both studies focused on connectivity seeded from the DLPFC and the subgenual cingulate cortex, a key region closely aligned with the DMN in depression.
Results: Chronically stressed subjects exhibited functional connectivity deficits within the frontoparietal ECN that were specific to the low resilience group; correlated with attention-shifting impairments; and were fully reversible after cessation of the stressor. Connectivity within the DMN was not affected. Similarly, patients with depression exhibited comparable connectivity deficits within the ECN prior to treatment, but they also exhibited specific, abnormal patterns of subgenual cingulate hyperconnectivity that were absent in stressed but otherwise healthy subjects. TMS normalized these patterns of subgenual cingulate hyperconnectivity but did not alter connectivity in the ECN, even in clinically euthymic treatment responders. These connectivity effects were highly consistent across individuals: Using binomial logistic regression, we discovered that depression-related patterns of abnormal connectivity could be used to reliably distinguish individual depressed patients and healthy controls in two independent cohorts, with a sensitivity and specificity in excess of 90%.
Conclusions: These findings indicate that stress effects on connectivity in the frontoparietal executive control network may be an early step in the pathogenesis of depression in vulnerable individuals, and resilience may depend on mechanisms that preserve normal connectivity in this network. Additional studies over longer intervals will be required to determine whether the persistence of these deficits in depressed patients after treatment is a marker of vulnerability for recurrence. Our results also identify unique patterns of subgenual cingulate hyperconnectivity that are specific to depression and may be implicated in the antidepressant mechanism of TMS. Finally, they underscore the potential for neuroimaging-based measures of functional connectivity to serve as biomarkers of active depression in individual patients.
Keywords: stress, depression, subgenual cingulate, prefrontal cortex, resting state fMRI
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M143. Reduced Functional Connectivity in Executive Networks Associated with Cigarette and Alcohol Use

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Background: Research has shown that alterations in functional connectivity are associated with chronic substance abuse and, in fact, we recently demonstrated that reductions in executive network strength negatively correlate with severity of alcohol use disorders. Deficits within executive control systems may undermine the ability to control alcohol and/or nicotine use. We now examined the functional connectivity of the executive control networks hypothesizing that cigarette smoking would also be associated with diminished network strength, above and beyond the effect of alcohol use. We further hypothesized that age may influence this relationship such that the detrimental effects of both nicotine and alcohol will be more pronounced in older subjects.
Methods: 610 right-handed individuals with a wide range of regular drinking and smoking underwent resting state functional magnetic resonance imaging and completed measures of substance use. The Right and Left Executive Control networks (RECN, LECN) were identified using previously defined functional regions of interest. Correlation matrices between nodes of each network were calculated and transformed to z-scores. Analyses tested the association of connectivity parameters with alcohol dependence and smoking, and tested whether these effects were influenced by age.
Results: LECN network strength was negatively associated with both alcohol use severity and amount of cigarette use controlling for age and motion across all subjects. In both the RECN and LECN, distinctly for older, but not younger, individuals, the same negative relationship was found between network strength and alcohol and nicotine use. Edges connecting dorsolateral prefrontal, middle frontal, parietal and temporal regions within the executive networks drove these relationships.
Conclusions: This study reports negative relationships between executive network strength and alcohol and cigarette use suggesting that both chronic drinking and smoking negatively impact brain connectivity. Diminished functional connectivity, related to long-term cigarette and alcohol use, may contribute to the etiology of substance abuse and dependence.
Keywords: smoking, alcohol, functional connectivity, resting state, executive control network
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M144. Functional Connectivity of the Intraparietal Sulcus Is Affected by Both Copy Number and Sequence Variation of the Williams Syndrome Gene LIMK1

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Background: The intraparietal sulcus (IPS) occupies a key position in the dorsal visual processing stream, which is responsible for coding information about 'where' objects are located. In previous work, the IPS has been shown to have structural and functional abnormalities in Williams syndrome (WS), a genetic disorder caused by hemizygous deletion of approximately 1.6 megabases on the long arm of chromosome 7 (7q11.23) and in which affected individuals display a hypersocial personality and significant visuospatial construction deficits. Although gene-gene interactions are likely to play an important role, one of the genes hemideleted in WS, *LIMK1*, has been particularly implicated in these deficits. Recent work in our lab has shown that the T allele of a *LIMK1* single nucleotide polymorphism (SNP), rs710968, is associated with structural changes of the IPS that are similar to those found in the copy number variation (CNV) of WS. We hypothesized that resting functional connectivity (eg coupling) of the IPS would also show association with both copy number variation and sequence variation of *LIMK1*.
Methods: To test for effects of CNV, 11 children with WS (average age 12.7 yrs [range 5.5–17.9 yrs], seven males), and 11 age- and sex-matched typically developing (TD) children (13.2 years [8.0–17.9 yrs], seven males) underwent resting fMRI scanning (TR 2 s, 1.875x1.875x3 mm, (2)x150 images - 10 min). Images were co-registered to each participant's anatomic image and were normalized to a mean template of all participants in MNI space. Seed based functional connectivity maps, from a seed in the IPS, were determined for each participant and compared across groups. To test for effects of sequence variation, DNA was obtained from two non-overlapping healthy volunteer samples studied on two different MRI scanners at different times. The initial sample consisted of 99 participants (32.6 yrs [18.8–56.6 yrs], 43 males), and the replication sample consisted of 32 healthy participants (39.0 yrs [22.0–61.3 yrs], 16 males). All participants were genotyped for the *LIMK1* rs710968 SNP and underwent resting fMRI scanning (initial sample: TR 1.596 s, 4x4x5 mm, 300 images - 8 min; replication sample: TR 2 s, 1.875x1.875x3 mm, (2)x184 images—12.3 min). Functional images were co-registered to each participant's anatomic MRI and aligned to MNI space. Seed-based functional connectivity maps, with a 6 mm seed region in IPS centered at $MNI_{x,y,z}$ (28, -68, 32), were determined for each participant and were compared between groups as a function of *LIMK1* SNP. Within-group t-tests were also performed on each group separately. Resulting maps were thresholded at $p < 0.05$, corrected for multiple comparisons using family-wise error.
Results: IPS functional connectivity in all groups revealed a robust network comprising dorsal and ventral visual processing streams. Examination of *LIMK1* CNV revealed that compared to TD children, those with WS exhibited reduced functional connectivity of the IPS with two regions early in the ventral visual processing stream bilaterally, specifically with visual areas V4 and MT/V5. In contrast, relative to TD children, those with WS exhibited increased

connectivity between the IPS and regions involved in social processing, including posterior cingulate, medial prefrontal cortex, and the temporo-parietal junction bilaterally. WS children also showed increased IPS connectivity with the left inferior frontal gyrus, left caudate, and left parahippocampal gyrus. For the examination of *LIMK1* sequence variation, the initial sample of 99 healthy volunteers genotyped at rs710968 contained 74 with a CC genotype and 25 with a TC genotype. The CC genotype, relative to the TC genotype, was associated with decreased connectivity between the IPS and right V4, bilateral inferior lingual gyri (BA18), left thalamus and left superior parietal lobule. The replication sample of 32 participants contained 24 with the CC genotype and 8 with the TC genotype. In this group, the CC genotype was again associated with decreased connectivity between the IPS and a right V4 region that was anatomically nearly identical with that identified in the initial sample. Genotype groups did not significantly differ in age or sex in either sample.

Conclusions: Previous work in WS has shown structural and task-related functional changes that occur preferentially in the dorsal visual processing stream. The gene *LIMK1* has been implicated in these abnormalities. Here, using resting-state fMRI, we report that, consistent with the cognitive phenotype of WS, IPS exhibits increased connectivity with brain regions involved in social processing, and decreased connectivity with regions involved in visuospatial processing. Additionally, changes in functional connectivity between IPS and early ventral stream regions (i.e. V5) were found to be related to sequence variation in *LIMK1*, with a SNP previously related to structural changes similar to those seen with WS. These changes are consistent with *LIMK1's* involvement in neuronal migration and axon guidance. Our results help to identify neurogenetic mechanisms underlying the WS phenotype, and, more generally, provide insight into the mechanisms by which genetic variability is translated through the brain into complex behavioral traits.

Keywords: Williams syndrome, LIMK1, intraparietal sulcus, fMRI, connectivity

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M145. In Anorexia Nervosa, Anxious Rumination Is Grounded in the Activation of Abnormal Interoceptive Insular Cortex

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Background: Remarkably little is known about the neural systems that underlie the disturbed body experience that characterizes anorexia nervosa (AN). For example, although AN patients often report somatic preoccupation with gut sensations (e.g., fullness or fatness), it remains unclear whether this reflects a cognitively-mediated obsession, or is a result of altered visceral interoceptive experience. Importantly, neuroanatomical and functional neuroimaging evidence both suggest that the insula cortex partially underlies visceral interoceptive awareness in healthy adults. As a result, the insula now plays a central role in theories that ground negative affect, such as fear and anxiety, in the autonomic state of the body. This is significant because, in addition to somatic preoccupation, AN is also associated with heightened fear and anxious rumination. Much clinical evidence demonstrates that elevated anxiety is a temperamental trait that broadly influences AN patients' responses to many classes of stimuli, not just those related to feeding and body image. Remarkably, however, there is little neuroscientific data to speak to which brain regions underlie this domain-general anxiety in anorexia. Given its role in interoception and the interaction of bodily states with emotion, the insula is a likely contributor to both the somatic preoccupation and heightened anxiety observed in AN.

Methods: We examined brain activity in adolescent and young adult females with restricting-type anorexia nervosa (AN-R) during attention to sensations in the heart, stomach, and bladder. All AN-R participants were weight-restored (BMI $>$ 18.5) but still receiving treatment. None of the participants, however, were currently receiving any psychotropic medications. Healthy female volunteers in the same age and weight range with no history of an eating disorder served as comparison subjects. To measure brain activity during interoception, participants underwent functional Magnetic Resonance Imaging (fMRI) while performing a task in which they focused their attention on sensations in their heart, stomach, or bladder. The bladder and heart were used as interoceptive targets that are not psychologically provocative in AN. An exteroceptive control task during which they focused on a visually-presented target was used as the baseline condition. To assess insula activity during anxious rumination, we also asked participants to perform a task during which they were presented with non-food/body-related anxiety-provoking words (e.g., '*peers*', '*family*', '*academics*', etc.) about which they were instructed to ruminate.

Results: Voxelwise analyses revealed a reliable Group X Interoceptive Source interaction ($p < 0.05$ corrected) in a region of the dorsal mid-insula that has been previously demonstrated to be a site where visceral information first arrives in the insular cortex. Subsequent analyses in this region, revealed that although the groups did not differ in activity during cardiac and bladder interoception, AN-R subjects exhibited lower activity in the dorsal mid-insula during stomach interoception than healthy controls. Having defined this as a region exhibiting abnormal interoceptive activity in AN, we then performed a region of interest (ROI) analysis to determine whether these voxels also exhibited abnormal anxiety-related activity in AN. Indeed, AN-R subjects exhibited significantly greater activity in this interoceptive region during anxious rumination than healthy control subjects ($p < 0.002$). Importantly, this effect was remarkably constrained to the dorsal mid-insula, with subsequent voxelwise analyses demonstrating that no other region of the insula exhibited reliably greater activity in AN-R subjects during anxious rumination as compared to healthy controls subjects.

Conclusions: These findings are consistent with the hypothesis that AN is associated with altered interoceptive experience of gastric sensations, and that this altered interoceptive experience contributes to the broader anxious temperament that characterizes many AN patients. In short, AN patients' experience of anxiety appears to be relatively more grounded in activity of abnormal interoceptive cortex. This finding may provide an important neural link between interoceptive experience of gastric distress and anxious temperament, which together may contribute to the development and maintenance of restricted eating patterns in anorexia nervosa.
Keywords: Anorexia nervosa, Interoception, Anxiety, Insula, fMRI
Disclosures: W. Simmons, Nothing to Disclose; K. Kerr, Nothing to Disclose; S. Moseman, Nothing to Disclose; J. Avery, Nothing to Disclose; J. Dobson, Nothing to Disclose; K. Burrows, Nothing to Disclose; N. Zucker, Nothing to Disclose.

M146. First HDAC PET Radiotracer Ready for Human Translation

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Background: Investigation of epigenetic changes - DNA methylation and post-translational modification of histone proteins - in the brain has provided new insight into the mediators of diverse CNS disorders. Numerous efforts have been made to develop noninvasive tools for imaging epigenetic modulators, for the detection and quantification of expression in vivo, which is critical to assess the efficacy of therapies targeting epigenetic mechanisms and to clarify the understanding of the mechanism enzyme dysfunction in disease. Histone deacetylase (HDAC) is one of the most intense investigated epigenetic enzymes, and recent studies have demonstrated that HDAC enzymes are associated with numerous brain dysfunctions and disorders. Clarifying the role of HDAC function in normal and disease biology has direct relevance to therapeutic development. Developing an imaging tool that permits detection and quantification of HDAC expression in vivo is critical to assess the efficacy of HDAC-targeted therapies and to clarify the understanding of the mechanism of HDAC enzyme dysfunction in disease. Positron emission tomography (PET) is an excellent tool for the in vivo quantification of HDAC biological processes as well as evaluation of the pattern of HDAC distribution in animals and human.
Methods: IC_{50} values were measured by Caliper EZ reader II system and calculated by Origion8 using 4 Parameter Logistic Model. The percent inhibition was plotted against the compound concentration, and the IC_{50} value was determined from the logistic dose-response curve fitting by Origin 8.0 software. Before the imaging studies, *Papio anubis* baboons was administered intramuscular ketamine (10 mg/kg) and intubated. MR-PET images were acquired in the combined MR-PET system (Siemens Medical Solutions) for brain scan and the Biograph mMR scanner (Siemens Medical Solutions) for whole body scan. Dynamic PET image acquisition was initiated followed by administration of [^{11}C]CN133. An MEMPRAGE sequence began after 30 min of the baseline scan for anatomic coregistration. The blocking experiment was carried out in which unlabeled CN133 was administered intravenously at 5 min prior to the acquisition at the dose of 0.01 mg/kg, 0.1 mg/kg, 0.5 mg/kg and 1 mg/kg. The CN133 precursor was labeled with [^{11}C]methyl iodine using GE tracerlab, and the average radiochemical yield was 9% (non-decay corrected to trapped [^{11}C]CH_3I). Chemical and radiochemical purities were $\geqslant$ 95 % with a specific activity 1.0 ± 0.2 Ci/μmol (EOB). In all scans, 4–5 mCi of [^{11}C]CN133 was administered to the baboon. Baboon PET/MR Image Analysis Volumes of interest (VOIs) were drawn manually as spheres in brain regions and Time-activity curves (TACs) were exported in terms of decay corrected activity per unit volume at specified time points.
Results: The hydroxamic acid-based HDAC inhibitor with the adamantine moiety was synthesized and its precursor was labeled with carbon-11 to be used as an imaging probe for PET imaging. CN133 shows good inhibition for HDAC 1, 2, 3 and 6 in the range of subnanomolar. Using PET-MRI, we determined that [^{11}C]CN133 exhibited high BBB penetration in *Papio anubis* baboons, was significantly blocked dose-dependently by the administration of unlabeled CN133 at the dose of 0.01 mg/kg, 0.1 mg/kg, 0.5 mg/kg and 1 mg/kg in the brain region with high HDAC density, demonstrating that [^{11}C]CN133 could detect the HDAC expression in brain in vivo. The NHP imaging study also revealed that the high uptake in the peripheral organs, such as heart, kidney and pancreas, and the uptake can be reduced by the pretreatment of unlabeled CN133 and other HDAC inhibitors (CN54 and SAHA).
Conclusions: To accelerate the application of this knowledgeto human disease, we successfully synthesized and characterized a brain penetrantPET radiotracer, termed [^{11}C]CN133, for quantifying a key element ofepigenetic regulation, the histone deacetylase (HDAC) family of proteins. PETstudies performed in conjunction with MRI evaluated the brain uptake of theseradiotracers, demonstrating excellent BBB penetration and displaying goodspecific binding in both brain and peripheral organs nonhuman primates. Thesedata reveal a reproducible and robust effect and we believe that our imagingagent, [^{11}C]CN133, could provide the first associations of classIHDAC density with brain function and dysfunction.Our non-human primate PET imaging resultsdemonstrating the brain penetrance of [^{11}C]CN-133 stand ascompelling evidence that this probe has a high likelihood of success as aCNS-penetrant HDAC imaging agent in humans.
Keywords: hydroxamic acid, HDAC inhibitors, epigenetic, PET, imaging
Disclosures: C. Wang, Nothing to Disclose; F. Schroeder, Nothing to Disclose; E. Holson, Nothing to Disclose; S. Haggarty, Nothing to Disclose; J. Hooker, Nothing to Disclose.

M147. Cannabis Use Is Associated with Nucleus Accumbens and Amygdala Abnormalities in Young Adult Recreational Users

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Background: Cannabis use is associated with impairments of cognitive functions, including learning and memory, attention, and decision-making. Animal studies show structural changes in brain regions underlying these functions, such as the nucleus accumbens (NAc), after exposure to Ä9-tetrahydrocannabinol (THC), but much less is known about the relationship between cannabis use and brain structure in humans. While some studies show volume reductions in the hippocampus, amygdala, and cerebellum, other studies have not shown a correlation between cannabis and brain volumes. Differences in methodology may have contributed to these mixed results, suggesting that using a variety of structural methods together to quantify brain morphology (i.e., gray matter density, volume, and shape deformation) may be important when studying the effects of cannabis on the brain.
Methods: We collected high-resolution T1 MRI scans on young adult cannabis/marijuana users (MJ) and matched non-using controls (CON) (all subjects 18–25 years old). MJ used cannabis recreationally, and were not dependent. We conducted three analyses of brain structure: (a) gray matter density (GMd), using voxel-based morphometry (VBM), (b) volume (total brain volume, grey and white matter volume, and regional volumes), to investigate gross volumetric differences between users and non-users, and (c) shape (surface morphometry), to investigate localized shape differences in vertices of subcortical structures.
Results: The whole-brain GMd analysis revealed greater GMd values in MJ than in CON in the left NAc extending to subcallosal cortex, hypothalamus, sub-lenticular extended amygdala (SLEA), and left amygdala. When we extracted data from each subject using peak ROI values, these differences remained significant even after controlling for age, gender, alcohol, and cigarette smoking. GMd in the left NAc and the left amygdala was further associated significantly with MJ drug use behaviors. The left NAc volume was larger in MJ subjects, mirroring the increase in GMd. Alterations in left NAc volume were associated with several MJ drug use measures. Significant shape differences were detected between MJ and CON using both voxelwise and ROI approaches in the right amygdala and left NAc; these differences remained significant after controlling for age, gender, cigarette smoking and alcohol use. These regions showed significant associations between shape measures and MJ drug use behavior. When we investigated the relationship between GMd, volume, and vertices, we found that multimodal relationships in CON were altered in MJ, particularly in the left NAc. In CON, there was a significant positive relationship between GMd and both volume and vertices in the left NAc; in the MJ, those relationships were largely insignificant.
Conclusions: Little is known about the effects of cannabis on the brain in young adult, recreational users. The current study demonstrates that even in young, non-dependent users, morphometric abnormalities are observable, many of which are dose-dependent. These data demonstrate that fundamental relationships among modalities that are observed in controls are absent in the MJ group, suggesting that marijuana use leads to a disruption of neural organization. These findings emphasize the importance of multimodal imaging, namely that (1) convergent evidence across modalities makes the most convincing case for a robust finding while at the same time acknowledging that (2) certain abnormalities may be more likely to be detected using one modality than another due to the different etiological sensitivities of different neuroimaging modalities. Although this study is cross-sectional and not longitudinal, correlations between multiple measures of morphometry and drug use measures provide evidence that marijuana use is associated with abnormal brain structure.
Keywords: cannabis, imaging, nucleus accumbens, morphometry, amygdala
Disclosures: J. Gilman, Nothing to Disclose; J. Kuster, Nothing to Disclose; S. Lee, Nothing to Disclose; M. Lee, Nothing to Disclose; B. Kim, Nothing to Disclose; N. Makris, Nothing to Disclose; A. van der Kouwe, Nothing to Disclose; A. Blood, Nothing to Disclose; H. Breiter, Nothing to Disclose.

M148. Predictive Classification of Pediatric Bipolar Disorder Morphometric Features of the Amygdala

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Background: Pediatric bipolar disorder (PBD) has a severe symptomatic presentation as compared to adult bipolar disorder (Ladouceur et. al, 2012). Discovery of objective *predictive* biomarkers able to guide therapeutic interventions is therefore imperative. Volumetric reductions of the amygdala in PBD have extensively been reported (Soares et. al, 2007). In this study, we investigated the utility of voxel-based morphometric features of the amygdala in predicting PBD using a Machine Learning (ML) approach.
Methods: 16 unmedicated patients with DSM-IV PBD and 16 Healthy controls matched for age, gender, and Petersen scores were scanned using a 1.5 T GE scanner. The study was approved by the local IRB and all participants and guardians gave informed assent and consent. DARTEL-SPM8 (Ashburner et. al, 2007) was used to segment, spatially normalize, and smooth T_1-weighted scans. The amygdala was delineated using the 'WFU_Pickatlas' (Maldjian et. al, 2003); resulting gray-matter probability values were used to train and test an Elastic Net machine learning model (Zhou et. al, 2005).
Results: As shown in figure 1, 25 out of 32 subjects were correctly classified. The model accuracy, sensitivity, and specificity were 78%, 75%, and 81%, respectively (χ^2, $p = 0.0014$).
Conclusions: This study confirms previous evidence on the existence of neuroanatomical abnormalities of the amygdala in PBD patients.
Keywords: neuroimaging, pediatric bipolar disorder, biomarkers, machine learning
Disclosures: B. Mwangi, Nothing to Disclose; D. Spiker, Nothing to Disclose; G. Zunta-Soares, Part 1: Research Grants - BMS, Forrest, Merck, Talks - ABBOTT, Pfizer; J. Soares, Part 1: Research grants - BMS, Forrest, Merck , Talks - ABBOTT and Pfizer

M149. Suicide Risk and Mood Regulation Deficits: Emotional Reactivity as an Exploratory Pathway

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Background: Suicide is a global disease burden, accounting for 1 million deaths annually worldwide. Mood lability appears to be a risk factor for suicidal behavior, independent of depression severity. Even so, a study has yet to evaluate emotion regulation (ER) deficits across neural measures of emotional reactivity. Moreover, although suicide rates among posttraumatic stress disorder (PTSD) are high, research evaluating ER deficits in association with suicidal behaviors in PTSD remains scarce. The present, exploratory study thus sought to (1) characterize suicide risk among patients with PTSD and (2) evaluate ER deficits and emotional reactivity as as an underlying neurobiological factor in association with elevated suicidal risk.
Methods: Twenty-two outpatients with DSM-IV-defined PTSD underwent fMRI to assess implicit emotion regulation (ER) using the Emotional Conflict Task. The present study constitutes a partial sample, and will be presented here; although data collection is ongoing and currently underway. The Emotional Conflict Task involved categorizing facial affect while ignoring overlaid affect words. Implicit ER is indexed by contrasting reaction times (RT) on incongruent trials preceded by another incongruent trial (iI), with incongruent trials preceded by a congruent trial (cI). Neural indices were calculated (RT, brain activation values) to compare trial-by-trial changes in emotion conflict regulation. Worst-point lifetime suicidal symptoms were assessed using the Columbia Suicide Severity Rating Scale (C-SSRS), which included Suicidal Ideation (SI) (0–5 score), SI Intensity (2–25 Score), and Suicidal Behavior subsections. Suicidal symptoms were hypothesized to be positively associated with deficits in implicit ER (i.e., RT times) and emotional reactivity of the limbic system. Specifically, patients with more severe suicidal symptoms were hypothesized to exhibit slower RT and differential emotional reactivity (i.e., increased amygdala, dampened vACC reactivity). Regression analyses were employed to evaluate proposed effects.
Results: Patients ranged in age from 33–61, with a mean age of 36.6 (SD = 9.50) years; 70% of the sample were female. Descriptive statistics revealed a high rate of endorsement for lifetime worst point CSSRS SI (M = 2.38, SD = 2.04), indicating a majority endorsing previous SI with consideration of a method for a suicide attempt (SA). CSSRS SI intensity also appeared high (M = 13.10, SD = 2.08). Approximately 26% of the sample endorsed an SA history, with 13% endorsing a multiple SA history. On the Emotional Conflict Task, regression analyses revealed that CSSRS lifetime worst-point SI predicted slower RT in adapting to emotional conflict; however, this finding emerged as an non-significant (ns) trend in the expected direction ($t = 1.980$, $\beta = 0.34$, $p = 0.057$). For brain activation values, elevated SI predicted increased L and R amygdala activation, as hypothesized ($t = 2.805$, $\beta = 0.522$, $p < 0.05$; $t = 3.868$, $df = \beta = 0.645$, $p < 0.01$, respectively); whereas, dampened vACC reactivity was not predictive of suicide risk ($p > 0.05$) in the present sample.
Conclusions: Preliminary findings are consistent with past work suggesting that impaired mood regulation may serve as a neurobiological underlying factor in suicidal behaviors. Elevated suicidal symptoms were associated with poorer emotional conflict adaptation, and predicted differential activation of neural susbstrates associated with reduced ER, specifically, increased amygdala reactivity. Emotion regulation deficits, by altering the processing of salient emotional information, are proposed to, in this way, lower the threshold for suicidal behaviors. Future research is warranted to replicate these findings within a larger sample, as power to detect effects was limited in the present pilot study. Since data collection is ongoing, repeat analyses are planned to test effects within a larger sample. Our findings underscore the importance of mood regulation factors as a potential neurobiological risk factor for PTSD and treatment target in suicide prevention.
Keywords: suicide risk, suicidology, implicit emotion regulation, emotional reactivity, PTSD, emotional conflict task
Disclosures: R. Bernert, Nothing to Disclose; M. Hom, Nothing to Disclose; M. Goodkind, Nothing to Disclose; K. Peng, Nothing to Disclose; D. Oathes, Nothing to Disclose; M. Primeau, Nothing to Disclose; A. Etkin, Part 4: Dr. Etkin has received a grant from Brain Resource, Inc. for taking part in the International Study to Predict Optimized Treatment in Depression (iSPOT-D).

M150. Relation of Diet, Exercise, and Body Mass Index to a Brain Imaging Biomarker of Plaques and Tangles in Non-demented Middle-aged and Older Adults

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Background: Adherence to a Mediterranean diet, regular physical exercise, and avoiding being overweight or obese are linked to superior cognitive function and lowered risk for developing Alzheimer's disease (AD). However, data on the influence of these modifiable protective factors on *in vivo* measures of AD neuropathology (i.e., amyloid-β plaques and tau tangles) in pre-dementia are limited.
Objective: In this study, we evaluated whether modifiable protective factors (dietary and physical activity habits and body mass index [BMI]) related to *in vivo* brain levels of plaques and tangles.
Methods: Retrospective and cross-sectional study including clinical, imaging and self-report measures. **Setting:** University research institute.
Participants: A volunteer sample of non-demented middle-aged and older adult subjects (n = 44, mean age = 62.6 + 10.7 years, range 40–85 years old) with either normal cognitive aging (n = 24) or mild cognitive impairment (MCI; n = 20). *Main Outcome Measure(s):* BMI > 25 was used as an indication of being overweight or obese, and self-reports were used to measure current degree of adherence

to a Mediterranean diet (single item question) and physical activity levels (International Physical Activity Questionnaire). Brain positron emission tomography (PET) scans were performed after injection of 2-(1-{6-[(2-[F18]fluoroethyl)(methyl)amino]-2-naphthyl}f, ethylidene) malononitrile (FDDNP), a molecule that binds to plaques and tangles. FDDNP-PET binding levels were reported as average values in brain regions increased in AD (frontal, parietal, medial temporal, lateral temporal, and posterior cingulate). Mixed models were estimated to determine whether BMI (normal *vs* overweight/obese) and current lifestyle (diet and physical activity) measures were related to cerebral amyloid plaque and tangle binding, and whether these associations differed for the two groups (normal aging vs. MCI).

Results: Overweight or obese MCI individuals had higher FDDNP-PET binding levels compared to those of normal body weight (1.11(.03) *vs* 1.08(.03), ES $=1.13$, $t(35)=-3.3$, $p=0.002$) but this effect was not observed in the normal aging group (1.08(.03) *vs* 1.08(.03), ES $=0.08$, $t(35)=-0.2$, $p=0.8$). Regular adherence to a Mediterranean diet at the time of assessment was associated with lower FDDNP-PET binding, regardless of cognitive status (1.07(.03) *vs* 1.09(.02), ES $=0.72$, $t(35)=-2.1$, $p=0.04$). Higher levels of current physical activity were associated with lower levels of FDDNP-PET binding in MCI (1.07(.03) *vs* 1.11(.03), ES $=1.04$, $t(35)=-3.1$, $p=0.004$) but not in normal aging (1.07 (.03) *vs* 1.07(.03), ES $=0.02$, $t(35)=-0.1$, $p=0.9$).

Conclusions: These findings support a relationship between modifiable risk/protective factors and *in vivo* measures of brain plaques and tangles in middle-aged and older individuals without dementia. The results are consistent with the hypothesis that adherence to a Mediterranean diet, regular physical activity, and maintaining normal body weight protect brain health as people age and may diminish accumulation of the neuropathology that defines AD.

Keywords: memory, nutrition, physical activity, obesity, FDDNP

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M151. A Twin Study Identifying the Origin of Abnormal Automatic Responses to Threat Related Stimuli in PTSD

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Background: Posttraumatic stress disorder (PTSD) is a common and often debilitating psychiatric condition that can occur after experiencing highly stressful events such as combat, violent crime, terrorist acts, abuse, or natural disasters. Research is beginning to identify biologic abnormalities, or 'markers,' found in PTSD, but one key challenge is determining whether such markers are acquired characteristics of the disorder or familial vulnerability factors that increase risk for developing PTSD after trauma exposure. This distinction is important because it has implications for how biologic markers might be used in the future. For example, a biomarker that is determined to be an acquired characteristic would be useless in pre-trauma screening for high-risk individuals; likewise, a biomarker that reflects a familial risk factor would not be a reasonable indicator of treatment response. Functional neuroimaging research has shown that the dorsal anterior cingulate cortex (dACC) is one of several brain regions consistently implicated in the pathophysiology of PTSD. Human and non-human animal studies have linked the dACC to fear learning and expression, both of which are abnormal in PTSD. Accordingly, individuals diagnosed with PTSD show dACC hyperactivity at rest as well as dACC hyperresponsivity during fear learning. Moreover, exaggerated dACC responses during cognitive interference have been shown to be a familial vulnerability factor for developing PTSD after trauma exposure. However, it is not known whether this abnormal dACC reactivity observed in PTSD is related to automatic responses to threat-related stimuli. In the current study, we used a probe that elicits automatic responses to characterize dACC responses to stimuli that predict threat. Using a unique design employing monozygotic (MZ) twins discordant for combat exposure (some of whom have since developed PTSD), we also aimed to characterize the origin of any observed functional brain abnormalities. Specifically, any functional abnormalities observed in participants diagnosed with PTSD and their cotwins (relative to participants without PTSD and their cotwins) would represent familial vulnerability factors for developing PTSD after combat exposure. Conversely, any abnormalities observed in combat-exposed participants (irrespective of diagnosis) would reflect the effects of combat exposure per se. Finally, any abnormalities observed in only the participants who have been diagnosed with PTSD would reflect acquired characteristics of PTSD.

Methods: Data from 19 male MZ twin pairs discordant for combat exposure were included in these analyses. Of the combat-exposed twins, eight met diagnostic criteria for combat-related PTSD. During fMRI scanning, participants viewed alternating 28-second blocks of fixation, masked fearful and masked happy facial expressions. During the face presentation blocks, emotional faces were presented for 33ms and immediately followed ('masked') by a neutral face.

Results: Participants with PTSD and their combat-unexposed cotwins without PTSD showed heightened dACC activation while viewing masked fearful facial expressions, consistent with the idea that dACC hyperreactivity to potential threat is a familial risk factor for developing PTSD after trauma exposure. We also observed a main effect of combat exposure, in which dACC responses to masked fearful faces were elevated in the combat exposed twins, irrespective of diagnosis. Thus, while combat exposure appears to generally amplify dACC responses to threat-related stimuli, individuals with PTSD and their identical combat-unexposed cotwins have exaggerated dACC responses, consistent with a familial vulnerability factor.

Conclusions: The findings suggest that exaggerated dACC activation associated with automatic evaluation of potential

threat is a familial vulnerability factor that may increase risk for PTSD following trauma exposure. The finding that trauma-exposure can amplify dACC activation (in individuals with and without PTSD) also emphasizes the importance of including a trauma-exposed control group in studies of PTSD.

Keywords: ptsd dorsal, anterior cingulate cortex, biomarkers emotion, fMRI

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M152. Brain Morphology in Adolescents and Young Adults at High and Low Risk for Alcohol Dependence: Separating Cause and Consequence

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Background: Emerging evidence suggests that brain morphology is a robust neurobiological feature of offspring from alcohol dependent families that may represent an intermediate phenotype forecasting increased susceptibility to develop alcohol and drug use disorders. Some volumetric differences appear to exist prior to the initiation of drinking. Abnormalities in brain circuits involved in emotion regulation and decision-making appear to be good candidates for investigation into the neurobiological underpinnings of addictive disorders. Both animal and human studies have found that the neurotoxic effects of alcohol may be accentuated in adolescent and young adult binge drinkers because the developing brain may be more sensitive to the deleterious effects of alcohol. With prospective data that spans adolescence and young adulthood, we have attempted to capture the influence of environmental exposure in order to separate the effects of familial/genetic underpinnings for addiction associated with a multiplex family history and those that may be due to personal alcohol and drug exposure. This approach provides the possibility of uncovering interactions of genetic and environmental effects. It is also important to determine if the effects of alcohol and other substance use in adolescence results in persistent effects in young adulthood.

Methods: A longitudinal follow up of adolescents and young adults from either multiplex alcohol dependence families or control families that spans over 20 years has offered the opportunity to perform repeated magnetic resonance imaging (MRI) scans and neuropsychological testing of a sub-sample of these individuals from 2004–2013. The MRI data set now includes a total of 380 scans. Of these,160 are first time scans, the remainder are second, third, and fourth scans. Neuropsychological testing has included the Iowa Gambling Task (IGT) that measures the effectiveness of decision-making. Diffusion tensor imaging (DTI) has been performed for 120 subjects.

Results: Familial risk effects were examined using manually traced volumes obtained for the amygdala and orbitofrontal cortex. Analyses were performed using sub-samples of children and adolescents (less than 21years) and young adults (over 21) while controlling for presence of substance use disorder. Familial risk effects were observed for the total amygdala volume in those under 21 ($p = 0.013$). The familial effects were lateralized with right amygdala volume being significantly different ($p = 0.006$) but left was not. Similarly, lateralized effects were seen for the OFC with right OFC volume reduced in high risk offspring under the age of 21($p = 0.029$). Survival analysis using the ratio of the OFC to amygdala volume showed a significant relationship to SUD outcome with those with the largest ratios having the best outcome. The effects of alcohol exposure was examined for subjects exposed as adolescents and evaluated in both adolescence and young adulthood. At an average age of 19.6 years (SD 6.3 years), we find 44.2% reporting at least one follow up year in which they engaged in binge drinking defined as 5 or more drinks on one occasion for males and 4 or more for females. Binge drinking by the time of the first scan was significantly related to total OFC volume ($p = 0.001$), and to amygdala volumes ($p = 0.0001$) Importantly, adolescent binge drinking showed a persistent effect on OFC and amygdala volume in young adulthood. White matter (WM) microstructure was investigated using diffusion tensor imaging (DTI) to determine the effects of familial risk and alcohol exposure on WM tracts. DTI analyses revealed an interaction between familial risk effects and alcohol exposure. These alterations in white matter integrity included the inferior longitudinal fasiculus (ILF), a major pathway between the temporal lobe and the occipital lobe that is thought to be involved in visual processing including emotionally salient information. Iowa gambling performance revealed significantly poorer performance over trials in high risk offspring suggesting a lack of ability to profit from previous experience on the task. IGT performance was inversely related to SUD survival time.

Conclusions: Neural circuitry nodes (OFC and amygdala) involved in emotion regulation and the ILF tract connecting the temporal lobe and occipital tract involved in processing the salience of visual emotional stimuli may differ in those at risk for alcohol dependence. Failure to attend to long-term costs and benefits during a decision-making task is associated with age of onset to develop SUD. Binge drinking in adolescence along with other substance use involvement further disturbs the neural circuitry involved in emotional processing and decision-making possibly rendering these individuals at continued risk for abusive patterns of drinking and drug use.

Keywords: substance use disorder; emotion regulation, orbitofrontal cortex, amygdala, DTI

Disclosures: S. Hill, Nothing to Disclose; W. Shuhui, Nothing to Disclose; H. Carter, Nothing to Disclose; R. Terwillinger, Nothing to Disclose.

M153. Unsupervised Identification of Population Patterns in High-dimensional Multimodal Neuroimaging Scans: A Data-driven Machine Learning Approach

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Background: Neuroimaging machine learning studies have recently succeeded in predicting *individual* subjects' brain states from high-dimensional neuroimaging scans (e.g. Health *vs* Disease—Mwangi, *et al*, 2012, or Treatment responders *vs* Non-responders - Doehrmann, *et al*, 2013). However, a majority of these studies have been *supervised*—meaning neuroimaging scans and corresponding target variables (e.g. Responders *vs* Non-responders) are used in developing the statistical model. This approach is not optimal in identifying 'unseen' population patterns especially when the researcher does not have pre-specified models. In this study, we set out to investigate the utility of an *unsupervised* machine learning approach in identifying 'unseen' population patterns and clusters that may exist in high-dimensional data.
Methods: Multimodal neuroimaging scans (T_1-weighted, Diffusion tensor imaging, T_2-weighted and Proton density) were acquired from 92 Healthy subjects (44 males, 48 females). Scans were pre-processed using Freesurfer, FSL and in house software routines following an atlas-based approach as described elsewhere (Walimuni and Hasan, 2011). Resulting features were fused and input into the t-distributed stochastic neighbor embedding (t-SNE) algorithm (Van der Maaten and Hinton 2008). t-SNE converts high-dimensional data into a matrix of pairwise similarities which capture the local structure of the high-dimensional data whilst revealing the global structure. The pairwise similarities between subjects' scan data were embedded into a low dimensional 2D space and further analyzed using the K-means clustering algorithm (see Figure 1).
Results: The unsupervised algorithm separated study subjects' neuroimaging scan data into two very distinct population clusters which were found to correspond to subjects' gender labels as shown in Figure 2(a). Cluster separation validity was highly significant with a silhouette width of 0.724 as show in Figure 2(b).
Conclusions: This method is able to uncover hidden or 'unseen' population patterns in high-dimensional neuroimaging scan data which is not possible with supervised multivariate or univariate methods. From a neuropsychiatric perspective this method may allow *data-driven* discovery of disease sub-types or sub-types of treatment responders.
Keywords: Multimodal Neuroimaging, Multivariate, Data-driven, Unsupervised Machine Learning, Research Domain Criteria, Big data.
Disclosures: B. Mwangi, Nothing to Disclose; K. Hasan, Nothing to Disclose; J. Soares, Part 1: Research Grants - BMS, FORREST and MERCK, Talks - ABBOTT and Pfizer.

M154. Electrophysiological and Anatomical Evidence for Two Distinct but Interacting Neural Circuit Abnormalities in the Auditory Cortex in Schizophrenia

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Background: A major goal of translational neuroscience is to identify neural circuit abnormalities in neuropsychiatric disorders that can be studied in animal models to facilitate the development of new treatments. Especially gamma (γ) oscillations in the electroencephalogram (EEG) have received considerable interest in this effort, as the basic mechanisms underlying these oscillations are understood and are conserved across species. Furthermore, abnormalities of γ oscillations have been reported in disorders such as schizophrenia (SZ), as well as animal models of this disorder, and post-mortem studies of SZ show abnormalities of neural circuits involved in γ generation. Sensory-evoked γ oscillations such as the 40-Hz auditory steady-state response (ASSR) are reduced in SZ compared to healthy controls (HC). Animal models based on NMDA receptor hypofunction demonstrate this deficit as well as an increase in spontaneous γ power, which has not been reported in SZ. Here we examined whether baseline γ power is increased in SZ, and the relationships between the 40-Hz ASSR deficit, baseline γ power, and gray matter volume in the auditory cortex in SZ.
Methods: Subjects were 24 chronic SZ (4 females) and 24 HC (4 females). Dipole source localization of dense electrode EEG data was used to examine oscillatory activity in the left and right auditory cortex during binaural auditory steady-state stimulation (20/30/40-Hz rates). Independent component analysis was used to remove ocular, myographic, and cardiographic artifacts. Phase locking factor (PLF) and spectral power were calculated from artifact-free single trial source estimates. 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 Heschl's gyrus (HG) as the region of interest. Clinical symptoms were assessed by SAPS and SANS.
Results: Consistent with previous reports, ASSR PLF was reduced in SZ compared to HC in the left hemisphere (LH) only for 40-Hz stimulation, and HG gray matter volume was reduced in SZ, with a larger reduction in the LH than the right hemisphere (RH). The novel findings of this study were: 1) Baseline γ power was increased in SZ compared to HC in both hemispheres for 20- and 30-Hz stimulation, and in the LH alone for 40-Hz stimulation. In contrast, resting γ power did not differ between groups. 2) Baseline γ power in the LH during 40-Hz stimulation was positively correlated with auditory hallucination symptoms. 3) ASSR PLF was inversely correlated with baseline γ power at 40-Hz during 40-Hz stimulation in SZ. 4) In SZ, HG gray matter volume in the LH was correlated with LH 40-Hz ASSR PLF and inversely correlated with LH baseline γ power during 20- and 40-Hz stimulation.
Conclusions: These data provide evidence for 2 distinct but interacting neural circuit abnormalities in SZ. One abnormality manifests as the 40-Hz ASSR deficit, and could be related to deficits in GABAergic neurotransmission. The other abnormality manifests as increased baseline γ power, possibly reflecting an increased excitation/inhibition balance related to NMDA receptor hypofunction on fast-spiking inhibitory interneurons. Increased baseline γ power resembles the increased spontaneous γ power seen in SZ animal models based on NMDA receptor hypofunction, demonstrating the clinical validity of this effect. The two circuit abnormalities interact during 40-Hz stimulation, when baseline γ power and ASSR PLF in the LH become

inversely correlated. These circuit abnormalities are also related to structural abnormalities in the context of reduced synaptic connectivity in the left auditory cortex.

Keywords: Electroencephalogram, Evoked γ, Baseline γ, Resting γ, Structural MRI, Auditory cortex, Schizophrenia, Auditory hallucinations

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M155. Dopaminergic Activity and Altered Insula Response to Sweet Taste Processing in Anorexia Nervosa

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Background: Several lines of evidence suggest that individuals with anorexia nervosa (AN) havealtered striatal dopamine (DA) function. Using the radioligand [11C]raclopprideand positron emission tomography (PET), we found that individuals recovered(REC) from AN (REC AN) have increased binding of DA D2/D3 receptors at baselinein the anterior ventral striatum relative to healthy controls (Frank, 2005; Bailer, 2013). DA disturbances in AN may contribute to an altered modulation ofappetitive behaviors. In fact we have found that REC AN subjects have asignificantly reduced fMRI signal response to the blind administration ofsucrose or water in the insula, anterior cingulate, and striatal regions(Wagner, 2008; Oberndorfer 2013) compared to healthy controls. The anterior insula,anterior cingulate, and orbital frontal cortex, which code the sensory-hedonicresponse to taste, all innervate a broad region of the rostral ventral-central striatum (Haber, 2006), where behavioral repertoires are computed based on these inputs.

Methods: In order to explore relationships between anterior insula and DAstriatal function, we have done a post-hoc analysis of our PET and fMRI dataand correlated baseline [11C]raclopride Binding Potential $(BP)_{ND}$ and BOLD signal in eleven REC AN whoparticipated in both the fMRI study using the sweet taste paradigm and the[11C]raclopride PET study.

Results: REC AN showed a negative relationship ($r = -0.81$, $p = 0.002$) between [11C]raclopride BP_{ND} in the right ventral putamen and BOLD response to tastes of sucrose in theright anterior insula.

Conclusions: Most people are uncomfortable when hungry and experience pleasure wheneating, whereas those with AN tend to be anxious when eating, and feel betterwhen starving and tend to avoid high calorie, palatable food. Our data suggestthat those individuals with the highest [11C]raclopride BP_{ND} - suggestive of a reductionin intrasynaptic DA concentrations and consistent with reduced CSF HVAconcentrations found in REC AN (Kaye, 1999) - in the ventral putamen had themost blunted BOLD response in the right anterior insula following a sweet tastestimulus. This finding suggests a lack of motivation or approach behaviors to salient stimuli, whichwould be consistent with phenomena of avoidance of highly-palatable foodcommonly seen in anorexia nervosa, as well as anhedonia and lack of motivationto change in general. The striatum, which plays a crucial role inlinking sensory-hedonic experiences to the motivational components of reward(Devinsky, 1995) has substantial anatomical connections to the anterior insula.Specifically, the ventromedial putamen serves as an ideal biomarker as it hasdirect inputs from the AI (Fudge, 2005). Animal studies indicate that DA in thestriatum and putamen correspond to motivational aspects of stimuli (Montague, 2004). The ventrolateral striatal sub-regions, including the ventral putamen,have been especially implicated in mediating behaviors involving eating (Kelley, 2002) particularly of highly palatable and high energy foods. Because fMRIsignals do not provide direct information about monoamine function, there isemerging interest in combining PET with fMRI.

Keywords: anorexia nervosa, positron emission tomography, fMRI, dopamine, insula, sweet taste processing

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M156. Reduced Prefrontal Gamma Band Power in Patients with Schizophrenia Studied with MEG During Working Memory

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Background: Abnormal prefrontal cortical activity is robustly observed in PET and fMRI studies of schizophrenia patients performing executive function and working memory tasks. Examinations of electrophysiological activity are an important complement to the more spatially precise studies of fMRI and PET since the time-course of neural activity can be more finely resolved and since activity at different frequencies may reflect distinct network dynamics or cell types (e.g., gamma band activity [GBA] and inhibitory interneurons), some of which may be more severely altered in patients than are others. However, while many studies have employed EEG to study working memory-related GBA abnormalities in schizophrenia, there are few studies using MEG. For the present work, MEG was combined with a beamforming algorithm (Vrba & Robinson, 2001), which offers improved localizability over EEG, in an effort to better localize GBA abnormalities during working memory in patients while they performed a hallmark working memory task.

Methods: Healthy controls ($n = 303$; age 31 ± 9; 170 women) and patients ($n = 82$; age 32 ± 11; 28F) with schizophrenia or schizoaffective disorder, diagnosed via clinician-administered structured clinical interview according to DSM IV criteria, were recruited as part of a large, ongoing observational study of patients, their siblings, and matched healthy volunteers. Healthy controls were screened and

excluded for history of alcohol/drug abuse, psychiatric illness, or family history of schizophrenia. Participants were excluded from analyses if they suffered any injury-induced loss of consciousness. Neuromagnetic activity was recorded at 600 Hz with a 275-channel whole head MEG system (CTF systems), using 3rd gradient noise cancellation. The N-back task consisted of a 0-back sensorimotor control task and a 2-back working memory condition, each of which was repeated 6 times in 20-second alternating blocks. Each event lasted for 1.8 seconds. Participants were also excluded from analyses if 2-back performance was under 25% (chance level for this task), if response rate was less than 80%, if head motion exceeded 5 mm, or if there were any large artifacts due to metal or excessive eye movements. Source localization was achieved using synthetic aperture magnetometry (Vrba & Robinson, 2001), a beamforming technique that estimates the pseudo-F ratio of gamma band (70–120 Hz) power in the 2-back condition relative to that in the 0-back condition in 5 mm3 voxels throughout the brain. A 500 millisecond time window following stimulus presentation was analyzed for each event in each condition. Each participant's 2back-0back contrast image was normalized for global activity and warped into standard MNI space using AFNI (Cox, 1996). These standardized images were included in t-tests comparing the group of healthy controls to the patient group. False discovery rate (FDR) with a q value of 0.05 was used to correct for multiple comparisons. Detailed medication status information was available for a subset of patients, and we conducted a regression analysis with chlorpromazine equivalent doses for this subset to test for medication effects.

Results: Because there was a significant difference in the proportion of males and females between control and patient groups (Fisher's exact test, $p<0.001$) and because performance on 2-back was significantly greater in the control group than in the patient group (means $= 89.6 \pm 13.1$ vs. 78.2 ± 17.7 percent correct, $p<1x10^{-6}$), effects of sex and 2-back accuracy were co-varied out. Additionally, because there was a slight, but significant between-groups difference in head motion (means = 1.9 mm vs. 2.4 mm, $p<0.005$), analyses were also performed with this variable as a nuisance variable. There was no between group difference in reaction time (means = 324.1 vs. 325.6 milliseconds). Comparing the two groups revealed significantly increased GBA in the controls relative to the patients in the right prefrontal cortex (t[383] = 3.2; 30, 18, 52), anterior prefrontal cortex (t[383] = 3.8; 6, 60, 8), and left inferior parietal cortex (t[383] = 3.6; −42, −42, 30) at $p<0.005$ FDR corrected. In the subset of patients who had complete medication information, no significant effect of chlorpromazine equivalent dose was found.

Conclusions: The working memory-related attenuation of the GBA response in patients agrees with previous findings and offers insight into schizophrenia-related neuropathophysiology. Qualitative similarities in the task-by-diagnosis interactions on GBA with those observed in previous PET and fMRI experiments raise the question of whether working memory-related prefrontal activation abnormalities observed in those modalities may be linked to altered GBA. Future multi-modal studies will help to clarify the relationship between electrophysiological and blood flow/metabolic studies of neural activity abnormalities in schizophrenia.

Keywords: Magnetoencephalography Working memory Schizophrenia Gamma

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M157. Resting State Functional Connectivity of the Habenula as a Biomarker of Depression and Treatment Response

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Background: A possible role for the habenula in major depression disorder (MDD) has been suggested before. The habenula is a major crossroads in the brain linking frontal regions and basal ganglia input to activity in the midbrain, including the ventral tegmental area, raphe nucleus, locus coeruleus and interpeduncular nucleus. Thus, habenular activity modulates the dopaminergic, serotonergic, noradrenergic and cholinergic systems of the brain. Abnormal habenular activity has been hypothesized to be associated with MDD. We wanted to study whether habenular resting state functional connectivity (RSFC) is affected by MDD, and whether habenular connectivity can be a biomarker for antidepressant treatment response. For antidepresant treatment we used ketamine infusion. Ketamine is an investigational MDD treatment that may exert an acute therapeutic effect on MDD patients.

Methods: We used a 3 T Siemens Trio MRI scanner to perform RSFC experiments (5 min of resting in the scanner while $3 \times 3 \times 3$ mm voxel BOLD data was collected) on 20 treatment-resistant MDD patients (day 1, patients were drug-free). On day 2, patients received either placebo or a ketamine infusion, and on day 3, RSFC was measured again using the same protocol. MADRS scores were used to measure MDD symptoms before and after ketamine treatment. RSFC connectivity was measured using the software CONN, placing a primary seed in the habenula and secondary seeds in areas hypothesized to be directly or indirectly connected to the habenula (nucleus accumbens, putamen and prefrontal cortex).

Results: On day 1, we found that the RSFC between the habenula and the nucleus accumbens negatively correlated to suicidal thoughts ($r^2 = 0.35$, $N = 20$). On day 3, we found that the change in RSFC between habenula and nucleus accumbens after ketamine (post- minus pre- RSFC) was positively correlated to the 24 h response to ketamine treatment ($r2 = 0.61$, $N = 11$).

Conclusions: We show here that a stronger correlation between the habenula and the nucleus accumbens is negatively correlated to suicidal thoughts in medication-free, treatment-resistant MDD patients. This is a somewhat counter-intuitive finding, since a strong functional connectivity between these areas may mean a stronger input of the habenula on dopaminergic activity and therefore

stronger negative affect. However, since this measurement was taken on drug-free patients, it must reflect the chronic, constitutive connectivity between the habenula and the nucleus accumbens. We hypothesize that a 'healthy' habenula is a good thing in the long run, since the habenula helps learning from mistakes by lowering dopamine during negative events. Thus, patients with stronger habenulo/accumbens connectivity in basal conditions may be better learners which may result in lower suicide ideation in the long run. In contrast, after acute ketamine treatment, a larger decrease in habenulo/accumbens connectivity correlated to better outcomes. We postulate that acutely, an effective treatment should be able to disconnect the habenula from the nucleus accumbens, so the patient would feel less impact from negative events. In conclusion, we postulate that habenulo/accumbens basal RSFC correlates with lower suicidal ideation in drug-free treatment-resistant MDD patients, and that the level of the inhibitory activity of ketamine on habenulo/accumbens connectivity correlates with better ketamine treatment outcome.

Keywords: Major depression Habenula Ketamine Biomarker

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M158. Lower Limbic System mGluR5 Availability in Cocaine Dependent Subjects: A High-Resolution PET [11C]ABP688 Study

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Background: Cocaine self-administration decreases type 5 metabotropic glutamate receptor (mGluR5)tissue concentrations in laboratory rats during early abstinence. These changesare thought to influence the drug's reinforcing properties and the varyingability of drug-related cues to induce relapse. Here, our goal was to measurebrain regional mGluR5 availability in recently abstinent cocaine dependenthumans.

Methods: Eight cocaine users meeting DSM-IV diagnostic criteria for current cocaine dependenceand nine healthy controls matched on age, sex, and lifetime cigarette smokingwere recruited from the general population. Past or current axis I disorders(including alcohol abuse or dependence) were among the criteria for exclusion. mGluR5availability (binding potential, BP_{ND}) was measured with positronemission tomography (PET HRRT) and the labeled high-affinity ligand,[11C]ABP688. A simplified reference region method was applied to the data,using the cerebellum as reference region. Separate ANOVAs were conducted for striatum (ventral, associative, sensorimotor), limbic (amygdala, hippocampus, cingulate, insula) and prefrontal regions of interest (ROI)(medial,dorsolateral, orbitofrontal).

Results: For striatal ROI, the ANOVA yielded a significant main effect of Group ($F = 5.61$, $p = 0.03$) and a Group $\times$ Region interaction ($F = 5.03$, $p = 0.013$) reflectingsignificantly lower BP_{ND} values in cocaine dependent subjects,-compared to controls, in the ventral striatum (left: $p = 0.006$; right: $p = 0.032$). The limbic ROI ANOVA yielded a Group $\times$ Region $\times$ Hemisphere interaction($F = 7.02$, $p = 0.001$) reflecting lower BP_{ND} values in the cocainedependent subjects in the left amygdala ($p = 0.036$), left cingulate cortex ($p = 0.05$) and right insula ($p = 0.052$). Finally, voxel-wise analyses identifiedgroup differences in left ventral striatum and amygdala, as well as leftlateral orbitofrontal gyrus and right dorsal striatum. Among the cocaine users,receptor availabilities in the somatosensory striatum and left amygdala wereinversely correlated with duration of abstinence (range: 2 to 14 days; $r = -0.72$, $p = 0.04$).

Conclusions: These results provide evidence of mGluR5 alterations in striatal and limbic regions inhumans during early cocaine abstinence. Since mGluR5 antagonists decreasecocaine self-administration in laboratory animals, receptor down-regulationmight reflect a compensatory response with implications for treatment.

Keywords: cocaine mglur5 PET addiction glutamate

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M159. Prefrontal Response to Visual Drug Cues Predicts Adherence to Extended-release Injectable Naltrexone in Heroin-dependent Individuals

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Background: Naltrexone (NTX) is a μ-opioid receptor antagonist with documented efficacy in subsets of opioid-dependent patients. However, the mechanisms of NTX-induced reduction in illicit opioid consumption have not been sufficiently elucidated. Drug-related cues are considered to be one of the causes of relapse to drug use. Injectable extended-release naltrexone (XR-NTX) is an approved treatment for opioid relapse prevention. We hypothesized that in detoxified heroin-dependent patients, XR-NTX will attenuate brain functional Magnetic Resonance Imaging (fMRI) response to heroin-related cues and that this response at baseline will predict subsequent adherence to XR-NTX.

Methods: Thirty-two heroin-dependent patients (aged 29.06 ± 8.47 years old, 15 female, 28 Caucasian, 2 African American and 2 Asian) were studied. Following non-opioid detoxification, participants received monthly XR-NXT (Vivitrol ®) for up to three months. Subjects underwent fMRI at 3 Tesla immediately before (PRE_XR-NTX) and 1–2 weeks after (ON_XR-NTX) the first XR-NTX, while viewing a set of heroin-related images (cues) (Langleben *et al* 2012). Within each MRI session, self-reported heroin craving was recorded before and after the cue exposure. Blood samples

for the levels of naltrexone and 6-beta-naltrexol, were collected at 1 week after the 1st XR-NXT, 2-weeks after 2nd XR-NTX and 3-weeks after the 3rd XR-NTX. Urine drug screen (UDS) and numbers of cigarettes smoked were collected weekly.
Results: Three injections were received by 54% of the participants, 7% had two injections while 18% dropped out after the first injection. Two-way repeated-measures ANOVA on the cue-induced heroin craving revealed significant main effects of *Cue Exposure* ($F(1,21) = 30.289$, $p < 0.0001$) and *Treatment* ($F(1,21) = 47.930$, $p < 0.001$), in the direction of the cue-induced craving reduction by NTX. During XR-NXT, cigarette consumption ($t(20) = 3.67$, $p = 0.002$) decreased significantly. There was no significant correlation between plasma concentrations of naltrexone or 6-beta-naltrexol and number of weeks (1 to 3) after injection. Repeated measures ANOVA applied to UDS results classified as one of 3 groups of drugs (opioids, cannabinoids and stimulants) showed significant interaction ($F(8,11) = 2.803$, $p = 0.008$) with Treatment Stage (i.e. PRE_XRNT, ON_XRNT = 1st, 2nd and 3rd XRNT and POST_XRNT). Percentage of opiate-positive UDS was lowest between the 1st and 2nd XRNT. Notably, cigarette consumption decreased significantly ($t(20) = 3.67$, $p = 0.002$) throughout the treatment period. A whole brain 2x2 ($z \geq 2.3$ cluster corrected at $p < 0.05$) ANOVA revealed significant main effects of *Cue* in the hippocampus and thalamus and *Treatment* in the anterior and posterior cingulate/precuneus, but no interaction between these factors. Whole brain correlation analysis revealed that activation in the dorsomedial prefrontal cluster (Brodmann areas 32, 11 and 10) at baseline was positively correlated with the number of XR-NTX received.
Conclusions: Our findings suggest continued vulnerability to relapse to opioids in the first three months of XR-NTX treatment of opioid dependence and support the need for longer treatment durations and studies with longer periods of follow up. Prior imaging studies indicate that medial prefrontal activation may mediate future intent, suggesting that the clinical value of dorsomedial prefrontal cortex response to drug cues predicting adherence to XR-NTX treatment warrants additional study. Finally, the observation that smoking is significantly reduced during XR-NTX therapy has implications for behavioral pharmacology of patients with dual opioid and nicotine dependence. Further research is needed on the efficacy, safety and potentially unique mechanisms of action of XR-NTX.
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Keywords: fMRI, Opioid, Heroin, Naltrexone, Vivitrol®
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M160. Amygdala Activation to Emotion Stimuli as a Predictor of Treatment Outcomes in Major Depressive Disorder: The International Study to Predict Optimized Treatment in Depression (iSPOT-D)

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Background: Previous functional neuroimaging studies implicate amygdala dysfunction in the pathophysiology of major depressive disorder (MDD) and responsiveness to antidepressants. It is unknown whether amygdala circuits predict a general response to antidepressants or a specific response to particular types of antidepressant. The International Study to Predict Optimized Treatment in Depression (iSPOT-D) is a practical trial coupled with multiple measures of brain function and, designed to identify predictors and moderators of outcome for commonly used antidepressant medications. Here we used functional magnetic resonance imaging (fMRI) to focus on amygdala circuits to test four aims: i) whether pre-treatment activation, elicited by emotional signals of threat, loss and reward, determines response outcomes; ii) whether prediction depends on a specific type of antidepressant; iii) if activation changes from pre-to post-treatment and iv) if activation implicated in outcomes also distinguishes patients from healthy controls.
Methods: In iSPOT-D, we have completed the assessment of the first planned testing phase: $n = 1008$ with MDD, and 336 matched healthy controls. MDD patients were randomized to one of three treatment arms: escitalopram, sertraline and venlafaxine-XR ($n = 336$ in each). Of these, approximately 10% ($n = 102$ MDD, $n = 34$ controls) were scanned using fMRI pre-treatment and at 8 weeks post-treatment follow up. We probed emotional processing by presenting facial expressions signalling threat (fear, anger, disgust), loss (sad) and reward (happiness), in both masked and unmasked paradigms. We used multivariate techniques (with family wise error correction) to determine clusters of amygdala activation which determined responder versus non-responder status at 8 weeks, and interactions with type of treatment. We then tested if activation from amygdala clusters involved in treatment outcome differed from pre-to post-treatment, and between patients and healthy controls. Response status was determined by $>= 50\%$ symptom improvement on the Hamilton Depression Rating scale.
Results: Responders showed amygdala hyper-reactivity while non-responders showed hypo-reactivity for emotions signalling threat and loss in the masked emotion paradigm. Pre-treatment amygdala activation in non-responders was

also reduced compared to healthy controls. Responder hyper-reactivity and non-responder hypo-reactivity was dependent upon treatment with SSRIs in particular. By contrast, responders showed hypo-reactivity to happy faces signalling reward in the unmasked paradigm. Antidepressant treatment worsened amygdala hypo-activity to sad expressions signalling loss in non-responders and increased activation to happy expressions signalling reward in responders.

Conclusions: A cohesive signature of amygdala activation predicts the general capacity to mount a response to antidepressants, and overlaps with the pathophysiology of depression itself. Prediction is most apparent for SSRI antidepressants, consistent with the role of the amygdala in serotonin pathways. To meet the practical translational goals of iSPOT-D, our next steps are to further personalize imaging-based predictive models by incorporating behavioral and physiological measures.

Keywords: depressive disorder, imaging, clinical biomarker trial, amygdala, antidepressants

Disclosures: L. Williams, Part 1: Consultant, Brain Resource , Part 2: Consultant, Brain Resource , Part 4: Sponsor of iSPOT-D, Brain Resource ; M. Korgaonkar, Part 4: iSPOT-D sponsor, Brain Resource ; S. Grieve, Part 1: Consultant, Brain Resource , Part 4: iSPOT-D sponsor, Brain Resource ; A. Etkin, Part 4: iSPOT-D sponsor, Brain Resource

M161. Relationship Between Central Mu-opioid System Response and Affect to Feeding Is Altered by the Pathophysiology of Obesity

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Background: The Central μ-opioid receptor (MOR) system has been implicated in the hedonic responses to food, and is a neurochemical system integrally positioned to regulate overconsumption of palatable foods. The relationship between central MOR systems and affective states and stress has been investigated in humans and rodent models but not under the context of the pathophysiology of chronic obesity and subsequent weight-loss. One of the most vexing problems with weight management is recidivism following weight-loss, and stress is known to be a potent mediator driving recidivism, including palatable food choice in emotional eaters and relapse in alcoholics. Since food consumption can be used as a coping strategy, a better understanding of the interplay among food consumption, stress, affect and central neurotransmitter systems is critical for long-term weight management. The response of central MOR system in obesity and weight loss and its relationship to affective states holds promise for targeted interventions in individuals at risk for weight regain.

Methods: To assess central MOR-system response to hunger and feeding in healthy-lean (lean-bsln; $n = 7$, BMI: 24 ± 1.6) and chronically obese men before (obese-blsn; $n = 7$, BMI: 38 ± 3.4) and after (obese-pwl; $n = 6$, BMI: 32 ± 1.8) diet-induced weight loss we utilized [^{11}C]carfentanil Positron Emission Tomography (PET) to measure MOR binding (non-displaceable binding potential: BP_{ND}). We also examined MOR binding following an overnight fast (fasted) and after consumption of a standard meal (fed) to assess dynamic activation of the MOR-system to acute feeding. For all whole brain voxel-by-voxel analyses threshold of significance was set at $p = 0.005$, uncorrected. Self-reported ratings of affect (PANAS) and hunger/craving (VAS) were collected for secondary analysis with extracted PET data.

Results: Several regions known to regulate homeostatic, reward, emotion and executive function were found to have differing levels of receptor availability in the fasted state and differences in MOR activation (fasted BP_{ND} > fed BP_{ND}) among lean and obese men. However, the right temporal pole (rTP)—implicated in regulation of emotion and affect—was the most robustly and consistently activated region in our analyses and is the region we focused on for comparisons with affect and hunger. We found MOR availability to be greater in lean-bsln-fasted compared to obese-bsln-fasted men in the rTP. Obese men had greater MOR receptor availability in the obese-pwl-fasted condition compared to obese-bsln-fasted in several brain regions, however lean-bsln-fasted men still had greater receptor availability in the rTP compared to obese-pwl-fasted. The standard, mildly-palatable, meal elicited robust central MOR-system activation (fasted BP_{ND} > fed BP_{ND}) in lean men in the rTP ($p = 0.002$, FDR). In contrast, obese men did not exhibit significant MOR-system activation to a standard meal in rTP, however diet-induced weight loss enhance MOR-system activation to a standard meal in rTP. To explore the relationship between affective response to the standard meal and MOR activation, extracted binding data from the rTP was used for secondary analysis with self-reported measures of affect and hunger in the fasted and fed state. The reduction in negative affect following feeding was inversely correlated MOR-system activation in response to the standard meal in lean men ($r = -00.97$, $p = 0.0002$). Chronically obese men did not show a relationship between central MOR-system activation in response to a meal and changes in affect at bsln ($r = -00.18$, $p > 0.0.7$) or pwl ($r = 0.65$, $p > 0.0.15$).

Conclusions: Collectively our results suggest that central MOR response to hunger and feeding is impaired in chronically obese, and that it is responsive to weight-loss. Further, central MOR response is not as robustly linked to affective response following a standardized meal in chronically obese men, and this dissociation may set the stage for compensatory overeating in an attempt to reduce negative affect. Beyond the pressing need to stem the tide of the current obesity pandemic, several lines of work have suggested that for individuals with comorbid psychiatric and metabolic disease (e.g. type-2 diabetes, obesity) management of mood and affect plays a large role in the self-care and subsequent course of metabolic disease and should therefore be considered when implementing treatment programs for these individuals. Our results indicate that the MOR system may be of value as part of a targeted intervention for those at risk of recidivism following weight loss, particularly for individuals who use food to cope with stress and modulate affect.

Keywords: opioid feeding obesity weight-loss affect

Disclosures: P. Burghardt, Nothing to Disclose; A. Rothberg, Nothing to Disclose; K. Dykhuis, Nothing to

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M162. Development of Cingulum Bundle White Matter in Pediatric Obsessive Compulsive Disorder

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Background: In treatment refractory OCD, anterior cingulotomy can be effective for some patients, with preoperative posterior cingulate cortex metabolism predicting better response (Rauch *et al*, 2001). Animal work shows the cingulum bundle to include afferent/efferent fibers from rostral anterior, dorsal anterior and posterior subregions of cingulate cortex *as well as* more distal cortical and subcortical regions. As such, the cingulum bundle is a complex white matter tract, likely comprised of distinct white matter pathways, serving distinct functions (Jones *et al*, 2013). Fractional anisotropy (FA), measured using DTI, reflectswhite matter coherence, and can be used to measure the integrity of white matter fibers within the cingulum bundle, as well as white matter projections throughout adjacent subregions of cingulate cortex. Given evidence for hyperactive dorsal anterior cingulate gyrus function in pediatric OCD, we hypothesized that, compared to healthy controls, young patients would exhibit increased FA in dorsal anterior cingulum bundle.
Methods: A 3 T GE MRI machine was used to collect DTI data from 36 patients with pediatric OCD (20 F; 14.7 ± 3.1 years) and 27 healthy control subjects (16 F; 14.1 ± 2.9 years), ranging in age from 8 to 19 years. 15 diffusion-weighted images ($b = 800$ s/mm2, two averages) were acquired for 39 slices (thickness = 3 mm, skip = 1 mm, TR = 9000 ms, TE = 82.3 ms, FOV = 22 cm). One non-diffusion weighted image ($b = 0$ s/mm2) was collected to transform the diffusion-weighted images to a template in MNI space. FA images were created, realigned to the FMRIB standard-space image and transformed into MNI space in FSL. Using tract-based spatial statistics (TBSS), a mean FA skeleton was created and thresholded at .2 for each participant. Regions of interest included the entire anterior to posterior length of right and left cingulum bundles (CB) from the Johns Hopkins University (JHU) White Matter Tractography Atlas, as well as rostral anterior, dorsal anterior and posterior subregions of adjacent cingulate cortex from the Automated Anatomic Labeling Atlas. Mean FA values were extracted from each ROI for each participant and entered into a linear regression to test the effects of group, age and group x age interactions in SPSS.
Results: A group x age interaction was observed for FA extracted from the right dorsal anterior cingulate cortex (dACC) ($p = 0.001$), driven by increases in FA with increasing age in pediatric OCD ($r = 0.64$, $p < 0.0001$), but not healthy controls ($r = -0.06$, $p = 0.76$). A trend-level group x age interaction was observed for the right JHU-defined CB ($p = 0.12$); as with the right dACC, FA in the right JHU-CB increased with age in the OCD ($r = 0.39$, $p = 0.02$), but not healthy control ($r = 0.08$, $p = 0.70$) group. An inverse effect of age ($p = 0.04$) and a trend-level group x age interaction ($p = 0.09$) was also observed for left rostral anterior cingulate but here, in contrast with the right dorsal anterior cingulate ROIs, the interaction was driven by a tendency towards age-related decreases in FA in the healthy ($r = -0.36$, $p = 0.07$), but not OCD ($r = 0.04$, $p = 0.83$) group. There were no other significant (or trend-level) effects of age, group or group x age interactions in any ROI.
Conclusions: Our results suggest atypical development white matter may localize to right dorsal anterior cingulate cortex in youth with OCD, with a pattern of protracted increase in FA in patients compared to healthy controls. Longitudinal work is needed to determine if increasing FA is more associated with persistence or remission of illness as youth with OCD continue to mature.
Keywords: ocd, anterior cingulate cortex, DTI, development
Disclosures: K. Fitzgerald, Nothing to Disclose; E. Reamer, Nothing to Disclose; Y. Liu, Nothing to Disclose; R. Welsh, Nothing to Disclose; S. Taylor, Part 1: I am affiliated with Neuronetics, conducting a study with them., Part 4: I am affiliated with Neuronetics, conducting a study with them.

M163. Prenatal Vigabatrin Exposure Attenuates Naloxone-Induced Withdrawal Behaviors in Neonates

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Background: The prevalence of Neonatal Abstinence Syndrome (NAS), a withdrawal disorder affecting newborns of opiate-addicted mothers, has increased substantially in the last few decades. Since the primary treatment for NAS is tapering doses of morphine or methadone, compounds with an addictive liability and known effects on brain development, we examined the potential of gamma-vinyl GABA (GVG, Vigabatrin) as an alternative pharmacologic strategy. GVG is an FDA approved medication for use in pregnant mothers. Since GVG has been shown to curb addiction in adult cocaine and methamphetamine users, we hypothesize that administration of GVG during the last six days of pregnancy may effectively attenuate naloxone-induced withdrawal behaviors in neonates.
Methods: Pregnant Sprague Dawley rats received either morphine (60 mg/kg/day SC; $n = 7$) or saline (SC; $n = 2$) throughout gestation. Of those who received morphine, 3 received GVG at 50 mg/kg/day (SC) and 2 received GVG at 25 mg/kg/day (SC) for the last 6 days of pregnancy. On post natal day 1 (PND 1), all neonates received an acute naloxone challenge, and their subsequent behavior was video-recorded. Three individuals, blinded to treatment, scored the frequency and severity of withdrawal behaviors of each neonate. The gross behavior scores for each treatment were averaged and compared.
Results: Neonates exposed to morphine throughout gestation exhibited marked withdrawal behavior following an acute naloxone challenge. This behavior was significantly greater than what was measured in animals exposed to saline alone ($p < 0.01$). Neonates who were treated with GVG

at 25 mg/kg/day during their last 6 days of gestation demonstrated withdrawal behavior similar to morphine controls. However, neonates who received GVG at 50 mg/kg/day during their last 6 days of gestation failed to demonstrate withdrawal behavior following an acute naloxone challenge. MicroPET imaging using ^{18}FDG, demonstrated that these same animals who received morphine alone throughout gestation had profoundly reduced brain metabolism upon reaching adolescence while those who received GVG at 50 mg/kg/day during their last 6 days of gestation had normal brain glucose scans.
Conclusions: These results suggest that GVG dose dependently attenates naloxone-induced withdrawal behaviors in animals exposed to morphine throughout gestation. Furthermore, GVG at 50 mg/kg/day during their last 6 days of gestation appears to attenuate decreases in brain glucose metabolism measured in these animals upon reaching adolescence. This strategy represents a novel, non-addicting, pharmacologic approach using an FDA approved drug that is safe for use in pregnant woman. With a nearly 3-fold increase in the incidence of NAS reported in the last decade, these findings have important implications for the development of novel treatment strategies for newborns suffering with NAS.
Keywords: opiates, neonates, vigabatrin
Disclosures: J. Kaczmarzyk, Nothing to Disclose; G. Santoro, Nothing to Disclose; S. Scherrer, Nothing to Disclose; S. Agorastos, Nothing to Disclose; J. Brodie, Nothing to Disclose; J. Carrion, Nothing to Disclose; K. Patel, Nothing to Disclose; R. Silverman, Nothing to Disclose; M. Choi, Nothing to Disclose; C. Veith, Nothing to Disclose; D. Mullin, Nothing to Disclose; S. Dewey, Nothing to Disclose.

M164. Group ICA Analysis of Smokers and Controls

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Background: Tobacco addiction is a major public health concern in the world. Current anti-tobacco therapies are far from satisfactory, mainly due to the lack of knowledge on the circuits mediating tobacco addiction and how these circuits are modified by acute and long term nicotine use. To address this question, we imaged the brain of sated and abstinent smokers and nonsmokers during the resting state for 5 min. Subjects were instructed to stay as still as possible in the scanner (eyes open or closed), while a fixation 'x' was presented in the field of view. The Resting State Functional Connectivity (RSFC) is a relatively new technique to study human brain function in which the functional connectivity among different brain areas is studied. RSFC has shown striking coincidence with networks necessary for certain types of behaviors. Group ICA has become an increasingly popular tool for analyzing resting state data, with new results emerging on subjects with a wide array of disorders.
Methods: All images were collected on a 3 Tesla Siemens Trio scanner. 35 smokers came for scans in sated and abstinent (overnight without smoking) conditions. In addition 45 nonsmokers were scanned once in an identical manner. Each subject at each scanning session underwent standard MP Rage sequence at resolution 1 by 1 by 1 mm followed by 5 min of resting state functional scans at 3.4 by 3.4 by 4 mm resolution. Data was analyzed using a standard preprocessing stream in SPM 8 (realignment, coregistration, segmentation, normalization and smoothing). A final step of motion regression was performed. Finally the Group ICA programs, GIFT and MANCOVAN were used to perform group ICA on the data to assess the effects of male vs. female, smoker vs. non smoker, and sated vs. abstinent conditions. An independent hierarchical clustering method was used to analyze the same set of subject data.
Results: We used group ICA and found significant differences for the totality of the ICA components. For male vs. female contrasts, the greatest differences were seen in supplementary motor area (male > female) and precuneus BA 7 (female > male). For smokers vs. nonsmokers the greatest difference was in bilateral Calcarine in Cuneus (non smokers > smokers). For sated vs. abstinent conditions, the group ICA analysis did not point to significant differences passing threshold. Using the hierarchical cluster analysis, we saw significant differences in number of networks between sated and abstinent smokers, as well as smokers vs. controls, particularly in supplementary motor area.
Conclusions: There has been a long literature on differences of addiction habits in males vs, females. It has been suggested that in females the habits associated with addiction have stronger importance than in males. Thus a difference in supplementary motor areas is not too surprising.
Keywords: Nicotine, Addiction, Group ICA
Disclosures: P. Baldwin, Nothing to Disclose; R. Salas, Nothing to Disclose.

M165. Resting State Functional Connectivity of the Dorsal Attention, Frontoparietal, Cingulo-opercular, and Default Mode Networks in Children with a History of Depression and/or an Anxiety Disorder

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Background: Functional networks are collections of brain regions with correlated activity both at rest and during cognitive tasks. Investigating changes in the operation of functional networks in psychiatric disorders may provide new perspectives on the neurobiology of these illnesses by offering testable models and providing novel targets for treatments. Depression and anxiety disorders may be associated with aberrations in multiple functional networks including the dorsal attention network (DAN), frontoparietal network (FPN), cingulo-opercular network (CN), and default mode network (DMN). The DAN, which includes the frontal eye fields and anterior intraparietal sulcus, is involved in the control of spatial attention. The DAN is a potential substrate of changes in attention associated with depression and anxiety disorders, including attention bias towards stimuli of negative valence. The FPN encompasses portions of dorsolateral prefrontal cortex and posterior intraparietal sulcus and is in involved in trial-level cognitive

control. Executive function deficits in depression and anxiety disorders suggest the FPN is altered in these disorders. The CN includes the dorsal anterior cingulate cortex and anterior insula and is involved in error monitoring and task-level cognitive control. Depression and anxiety disorders are linked to altered error monitoring, implicating the CN. The DMN includes regions in medial prefrontal cortex, posterior cingulate cortex, medial and lateral parietal cortex, and portions of the temporal lobe. The DMN may implement self-referential processes, and many studies have demonstrated DMN alterations associated with depression. While most evidence concerning functional networks is from adults, depression and anxiety are increasingly viewed as disorders of neurodevelopment. It is important, therefore, to test whether children with these disorders have alterations in functional networks. We hypothesized that children with a history of depression and/or anxiety disorders would exhibit differences in functional connectivity of the DAN, FPN, CN, and DMN relative to children without a history of any psychiatric disorder.

Methods: Subjects were ascertained at ages 3–6 years as part of a longitudinal study of childhood-onset depression. Here, we describe resting state functional neuroimaging data collected when the children were 8–12 years old. We divided subjects into those with a history of depression and/or an anxiety disorder (ANX/DEP) and subjects without any history of a psychiatric disorder (HC). Data were volume censored to reduce artifact from movement, resulting in analyzable data from 30 DEP/ANX children (mean age 10.1 years, 12 male) and 42 HC children (mean age 10.1 years, 20 male). We selected 4 or 5 regions from each functional network (DAN, FPN, CN, DMN), yielding 6 or 10 unique within-network connections per network. We computed the resting state functional connectivity strength (RSFC) for each within-network region-region pair as the Pearson's correlation coefficient. We compared RSFC strength for each functional network between DEP/ANX and HC using repeated measures ANOVAs, with diagnostic category as a between subject factor and individual (region-to-region) connection strength as a repeated measure.

Results: The DAN was the only network exhibiting a main effect of group ($p = 0.016$), with DEP/ANX having lower DAN functional connectivity relative to HC. For both the CN and DMN, there was a significant group by connection interaction ($p < 0.01$). In the CN, the functional connection between the left and right anterior insula regions was significantly lower in ANX/DEP relative to HC ($p = 0.02$). In the DMN, the functional connection between posterior cingulate cortex and medial prefrontal cortex was significantly higher in ANX/DEP relative to HC ($p = 0.01$). No significant results were found in the FPN.

Conclusions: Children with a history of depression and/or anxiety had decreased RSFC strength across all connections of the DAN, consistent with alterations in attention in these disorders such as attention bias towards stimuli with negative valence. Individual connections within the CN and DMN were also altered, perhaps paralleling changes in error monitoring and self-referential processes, respectively. These findings suggest that all functional connections of the DAN and specific functional connections within the CN and DMN may be targets for treatment development in depression and anxiety disorders.

Keywords: Functional Networks, Resting State, Depression, Anxiety, Children

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M166. Longitudinal fMRI Study of Quetiapine in Bipolar Mania

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Background: Affecting approximately 1–2% of the United States population, bipolar disorder is characterized by affective instability that may manifest in manic and depressive episodes. Although it remains a leading source of disability worldwide, the neuropathophyisology of bipolar disorder remains poorly understood. Recent neuroimaging findings however, suggest that manic episodes are associated with a loss of ventrolateral prefrontal cortex (VLPFC) modulatory control over regions involved in emotional expression including the amygdala and linked, subcortical structures. These functional changes are marked by decreased activity in the VLPFC, and increased activity elsewhere in the neuronal circuit. Over the last several years, there has been an explosion in the number of clinical interventions FDA-approved for bipolar mania–many of them atypical antipsychotic medications. The mechanism-of-action of these medications however, remains poorly understood. While at least some previous imaging studies suggest that treatment response may be marked by disparate neurochemical changes in portions of the anterior limbic network (ALN), relatively few studies have prospectively examined the immediate effects of these medications on functional activation in patients with bipolar mania, or parsed the interaction between functional changes and symptomatic improvement. Further, while some studies have found disparate neurophysiological changes between 'responders' and 'non-responders,' patient improvement is more typically a continuous, rather than dichotomous, variable. In this study we examined neurofunctional changes in a cohort of patients with bipolar mania over eight weeks, compared with healthy subjects. In addition, we tested the relationship between symptomatic changes and medication-related functional activation of core portions of the ALN. We hypothesized that symptomatic improvement would be associated with increased VLPFC activation and decreased activation of amygdala and subcortical structures during performance of an affective task.

Methods: Following written, informed consent, 30 subjects meeting DSM-IV criteria for bipolar disorder, type I, currently manic, and 15 healthy subjects participated in research procedures. Diagnoses were made, or excluded, using the Structured Clinical Interview for DSM-IV (SCID-IV). All subjects were clinically assessed using the Young Mania Rating Scale (YMRS) at baseline and week eight.

Bipolar subjects were medication-free at baseline and treated clinically with open-label quetiapine over eight weeks. All subjects participated in fMRI scans at baseline and after eight weeks of treatment. During the fMRI scans, subjects performed a Continuous Performance task with emotional and neutral distractors (CPT-END). The CPT-END is a visual odd-ball task, during which subjects view squares (80%) or circles (20%); subjects are instructed to press the number '2' on a button box when they view the former, and the number '1' when the latter appears. In addition, some squares contained pictures of an emotional or neutral nature. All scans were obtained using the UC CIR 4.0 Tesla Varian Unity INOVA Whole Body MRI/MRS system. Functional activation associated with exposure to emotional pictures during the CPT-END was calculated on a voxel-by-voxel basis using analysis of functional neuroimaging (AFNI). Regions-of-Interest (ROIs) were defined based on Talairach coordinates using AFNI, and ROI masks applied to the fMRI data obtained. Changes in activation in bipolar versus healthy subjects were examined using a 2X2 ANOVA. Interactions between YMRS and regional brain activation in bipolar subjects were calculated using a mixed model design. All statistical analyses were done using SPSS. Significance was defined as $p < 0.05$.

Results: At baseline, bipolar and healthy subjects differed only in the functional activation of the left globus pallidus ($p = 0.05$). A group (bipolar/healthy subjects) by time interaction was observed in functional activation during exposure to emotional stimuli in both the left ($F = 3.95$; $p = 0.05$) and right ($F = 5.38$; $p = 0.03$) VLPFC, and the left globus pallidus ($F = 4.51$; $p = 0.04$). There was no group by time interaction observed in the left ($p = 0.98$) or right ($p = 0.73$) amygdala. YMRS significantly interacted with changes in functional activity in the right ($F = 15.33$; $p = 0.003$), but not the left ($p = 0.85$) VLPFC, or in the left globus pallidus ($p = 0.39$). There was a near-significant effect observed in the left ($F = 3.55$; $p = 0.07$), but not right ($p = 0.16$) amygdala.

Conclusions: These findings suggest that atypical antipsychotic medications such as quetiapine may exert much of their influence on prefrontal brain regions involved in emotional modulation, rather than on regions such as the amygdala directly involved in emotional expression. Further, symptomatic response may be related to lateralized prefrontal effects—and 'downstream effects' on amygdala activity. Outside of the globus pallidus, changes in subcortical activity did not significantly differ between bipolar and healthy subjects; and no interaction with YMRS was noted for these structures. These findings are consistent with at least some previous studies suggesting changes in VLPFC and amygdala activity in medication responders, but extend previous findings by more explicitly modeling interactions between YMRS score and functional activation over time.

Keywords: bipolar disorder, mania, quetiapine, fMRI

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M167. Increased Glutamate in the Dorsal Anterior Cingulate Cortex Is Associated with Anxiety Symptom Domain in MDD with High inflammation

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Background: Previous work using a variety of inflammatory stimuli and multiple functional imaging modalities have consistently indicated that cytokines target dorsal anterior cingulate (dACC) and basal ganglia regions, resulting in behavioral symptoms including anxiety, depression and fatigue. Data from several sources indicate that cytokines might induce neural activity changes in dACC and basal ganglia tissues by decreasing synaptic clearance of the excitatory neurotransmitter glutamate. Preliminary data indicate that four weeks of exposure to the innate immune cytokine interferon (IFN)-alpha was associated with significant increases in normalized glutamate concentrations (to creatine, Glu/Cr) in dACC and left basal ganglia regions, which in turn were correlated with increases in depression and fatigue and reduction in activity levels and motivation. However, it is unclear if similar Glu/Cr changes in the dACC and left basal ganglia are observable among patients with major depression with high inflammation. We hypothesized that Glu/Cr ratios will be increased in dACC and left basal ganglia among depressed patients with high inflammation (c-reactive protein - CRP $\geqslant 3$ mg/L) patients compared to depression with low inflammation (CRP < 1 mg/L) and that the increase in dACC will be correlated with the levels of anxiety, depression and fatigue symptoms.

Methods: Twenty patients with major depressive disorder (as determined by SCID) and free of psychotropic medication or unstable medical conditions participated in the study. Seven patients with increased inflammation underwent MRS scanning, blood draws and psychiatric assessments. Thirteen MDD patients with low inflammation served as controls and were studied in similar fashion. Study assessments included the State-Trait Anxiety Inventory (STAI), 17-item Hamilton Depression Rating Scale (HDRS), and Multidimensional Fatigue Inventory (MFI). An anatomical T1-MPRAGE scan was obtained using Siemens Trim Trio Scanner to enable identification of voxels. The MRS settings were: TR/TE/NS = 3000/30/128, voxel sizes = 20x30x10 mm^3 in the dorsal anterior cingulate cortex and 17x30x17 mm^3 in the left and right basal ganglia. Post processing was done using the LC Model. Glutamate values were normalized to creatine (Glu/Cr) for use in data analysis. A comparison of creatine (Cr) and its metabolite phosphocreatine (PCr) values revealed no significant differences between the high and low inflammation groups.

Results: The Glu/Cr ratio in the dorsal anterior cingulate cortex was significantly higher in patients with depression and high inflammation compared to the low inflammation group ($p<0.001$). The Glu/Cr ratio in dACC was also positively correlated with scores on the STAI (Spearman $r=0.52$, $p=0.018$). Of note, patients with depression and high inflammation had significantly greater mean body mass index (BMI) compared to patients with low inflammation ($p<0.001$). Nevertheless, the correlation between dACC Glu/Cr and STAI was independent of the effects of age, sex, race and BMI. There was no association between dACC Glu/Cr and ratings on the other behavioral scales. No statistically significant changes in Glu/Cr ratios in the left and right basal ganglia were noted.
Conclusions: Inflammatory cytokines have been shown to reduce function of glutamate transporters on astrocytes as well as increase astrocyte glutamate release. A large volume of literature exists linking fear experience, expression, and anxiety states with glutamate neurotransmission. Perturbations in ACC functioning induced by cytokines might lead to hyper responsiveness of limbic circuits to negatively biased social cues resulting in anxiety.
Keywords: glutamate imaging, cytokines, cingulate anxiety
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M168. Intravenous Morphine Self-administration Reduces In Vivo Regional Glucose Utilization (18FDG-PET) and Accelerates Fear Extinction Behavior in Rats

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Background: Chronic exposure to drugs of abuse can lead to changes in brain energy metabolism and addiction-related behavior. Also, withdrawal from these drugs can increase anxiety and stress responses which may contribute to a relapse to drug use. However, *in vivo* brain energy metabolism and fear-related behavior during withdrawal from chronic opiate use are largely unknown. A few studies have shown that withdrawal from repeated experimenter-administered morphine was associated with impaired fear extinction in rats (Gu *et al*, 2008; Gong *et al*, 2010).
Methods: Using a clinically relevant intravenous morphine self-administration (MSA) paradigm, we studied the effects of morphine withdrawal on *in vivo* regional glucose metabolism and fear behavior in rats. Male Sprague-Dawley rats self-administered morphine (0.5 mg/kg/injection) intravenously on a daily session (4 h/day, 5 days/week) for 3 weeks. Following three weeks of the MSA, animals were tested for Pavlovian fear conditioning and fear extinction during withdrawal from morphine. *in vivo* regional glucose uptake was measured using a combined [18F]fluoro-2-deoxy-D-glucose positron emission tomography (^{18}FDG-PET) and computed tomography (CT) scan before and after the chronic MSA.
Results: We found that morphine dependent animals did not show differences in fear learning but showed accelerated fear extinction when the animals were re-exposed to the fear cue. This fear extinction was persistent at least for one week. In morphine dependent animals, *in vivo* glucose uptake was decreased in brain regions such as the hypothalamus and the brain stem as compared to the baseline levels. A morphine challenge (0.5 mg/kg) during the withdrawal induced a robust locomotor stimulation and increased *in vivo* glucose uptake in the nucleus accumbens, the amygdala and the brain stem.
Conclusions: Spontaneous withdrawal from chronic morphine use and re-exposure to the drug may have drastic effects on glucose metabolism in brain regions involved in drug dependence and anxiety behavior. This may partially explain the mechanism of the abnormal fear extinction behavior observed in morphine dependent animals. Using a clinically relevant animal model of drug addiction and a non-invasive brain imaging technology (PET), we demonstrated the utility of studying the important relationship between brain energy metabolism and addiction behavior. The current findings may have important clinical implications because morphine is widely used as an analgesic and has a high abuse potential in the population. A better understanding of the biological basis of vulnerability and resilience to opioid dependence and stress-related behavior will benefit the development of a novel treatment strategy for a comorbid anxiety and substance use disorders.
Keywords: Opioid dependence, In vivo Brain imaging, Drug self-administration, Fear extinction, Anxiety disorders
Disclosures: T. Le, Nothing to Disclose; R. Selwyn, Nothing to Disclose; R. Ursano, Nothing to Disclose; K. Choi, Nothing to Disclose.

M169. Brain Diffusion Tensor Imaging and 31P Spectroscopy of *In Vivo* Tau P301L Toxicity Mechanisms

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Background: Alzheimer's disease (AD) is the 6th leading cause of death in the United States, with an estimated 5.3 million Americans currently living with the disease. There is growing support for a role of tau protein in early degeneration in AD and in mice with inducible tauopathy. Elevated CSF concentrations of tau have been measured in AD and pre-AD stages, which also show white matter (WM) structural damage. Increased levels of hyperphosphorylated tau may contribute to microtubule destabilization, disrupt axonal transport and protein trafficking, and interfere with the myelinating functions of oligodendrocytes. However, it has been difficult to demonstrate an *in vivo* causal role of hyperphosphorylated tau in neuropathology, as measured clinically by diffusion tensor imaging (DTI). Moreover, the sequence of *in vivo* neurodegenerative changes predating cognitive deficits and tangle pathology needs further

investigation. The present study begins to addresses these gaps. The main hypothesis tested was that the expression of mutant P301L tau results in specific *in vivo* neurodegenerative alterations reflecting early neuronal and white matter (WM) pathology.

Methods: Using *in vivo* diffusion tensor magnetic resonance imaging (DT-MRI) at 11.1Tesla we measured age-related alterations in WM diffusion anisotropy indices in a mouse model of human tauopathy (rTg4510) and nontransgenic (nonTg) control mice at 2.5, 4.5 and 8 months of age. We also used ^{31}P magnetic resonance spectroscopy at 17.6Tesla in a cohort of 8-month old mice to investigate the potential role of membrane phospholipid turnover in P301L tau-mediated pathology.

Results: Similar to previous DT-MRI studies in AD subjects, 8 month-old rTg4510 mice show lower fractional anisotropy (FA) values in WM structures than nonTg. The low WM FA in rTg4510 mice was observed in the genu and splenium of the corpus callosum, anterior commissure, fimbria and internal capsule and was associated with a higher radial diffusivity than nonTg. Estimated diffusion shape measures confirmed an increase in spherical shape diffusion with a decrease in linear shape diffusion in WM areas. Interestingly, rTg4510 mice showed lower estimates for the mode of anisotropy than controls as early as 2.5 month suggesting that this diffusivity estimate is detectable at an early stage of tauopathy. 31P MRS results indicared a dramatically lowered metabolite to phosphocreatine ratios for phospho-mono- and diesters (PME, PDE), and inorganic phosphate in rTg4510 mice compared to nonTg.

Conclusions: A persistent finding is that fractional anisotropy (FA), one of the DTI indices of the directionality of water diffusion, is reduced with age, and severely so in AD. FA reductions occur in association with increased *radial* (D_R) and *mean diffusivity* (D_{ave}), and reduced *mode of anisotropy* (A_{MO}). The rTg4510 mouse expresses P301L tau in forebrain regions including the hippocampal formation, temporal lobe, frontal cortex, amygdala, which are areas reported to show reduced WM FA in DTI studies of AD and MCI. Within axons, tau-related destabilization of microtubules may be an integral part of axonopathy and neuronal loss. Also, increased microgliosis near myelinated axons, breakdown of myelin, and axonal loss may underlie reduced FA. The MRS-detectable membrane phospholipids and catabolites include phosphodiesters (PDEs), phosphomonoesters (PMEs), plasmalogens (Pls), docosahexanoic acid (DHA), sulfatides (STs) and others that are enriched in WM and neuronal membranes. It is proposed here that increased expression of P301L tau involves early stage deposition of molecular iron species, which may in turn precede reductions in WM integrity and antioxidant membrane phospholipids Our data support a role for the progression of tau pathology in reduced WM integrity measured by DT-MRI. Further *in vivo* DT-MRI studies in the rTg4510 mouse should help better discern the detailed mechanisms of reduced FA, and the specific role of tau during neurodegeneration.

Keywords: Tauopathy; neurodegenerative disease; Alzheimer's disease; FTDP-17; rTg4510; diffusion tensor MRI; white matter integrity

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M170. *In Vivo* Diffusion Tensor Imaging Evidence for Reversible White Matter Microstructural Integrity Disruption with Binge but Not Chronic Ethanol Exposure

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Background: Disruption of white matter microstructural integrity, measured with in vivo diffusion tensor imaging (DTI), is a feature of chronic alcoholism. Here, DTI was used to determine the differential effects of acute versus chronic ethanol exposure on white matter structural integrity in two distinct longitudinal rodent models of alcoholism.

Methods: *Acute binge experiment.* Wild-type male Wistar rats (8 EtOH, 10 Dextrose), weighing 334.83 ± 3.7 g at baseline, were exposed to binge ethanol via oral gavage. Animals were scanned on 3 occasions: DTI 1—pre-treatment baseline; DTI 2—followed 4-days of oral gavage of EtOH (to blood alcohol levels (BALs) of 291.72 ± 7.6 mg/dl) or Dextrose; and DTI 3—followed one week of recovery. *Chronic vapor experiment.* Wild-type male Wistar rats (8 EtOH, 10 Air), weighing 292.8 ± 38.0 g at baseline (DTI 1), were exposed to chronic ethanol via vapor chamber. Ethanol was administered intermittently (i.e., 14 h/day) at escalating doses for 16 weeks until average BALs of ~300 mg/dl were achieved by day 112. An additional 8 weeks (56 days) of alcohol exposure escalated BALs to ~450 mg/dl with the intention of testing whether higher BALs for a longer period of time would result in further effects on brain. *DTI acquisition.* Imaging experiments were conducted on a clinical 3 T GE Signa human MR scanner equipped with a high-strength insert gradient coil. For the acute binge experiment, six noncollinear directions (b = 1464 s/mm2) with alternating polarity and one b = 0 s/ mm2 image were acquired in the axial plane, coronal to the magnet system bore. For the chronic experiment, six noncollinear directions (b = 1009 s/mm2) with alternating polarity and one b = 0 s/mm2 image were acquired in the coronal plane, transaxial to the bore. *Fiber Tracking.* The native DTI data were used for quantitative fiber tracking. Corpus callosum genu and splenium and bilateral hippocampal fimbria-fornix targets were identified on fractional anisotropy (FA) images. Sources were parallel planes, 10 pixels lateral to either side of the corpus callosum or anterior/posterior to the hippocampus. Quantification methods for mean FA and mean diffusivity (MD) of fibers were similar to those used in human experiments. Identical procedures were used to fiber track FA and MD of the corpus callosum genu and splenium and left and right hippocampal fimbria-fornix for both the binge and chronic experiments.

Results: *Acute binge experiment.* Repeated-measures ANOVAs for the FA of each fiber track yielded group-by-session interactions for the genu ($F(2,32) = 4.625$, $p = 0.0172$) but not the splenium ($F(2,32) = 0.273$, $p = 0.763$). Interactions

were also significant for both the left ($F(2,32) = 5.731$, $p = 0.0075$) and right ($F(2,32) = 4.363$, $p = 0.0211$) hippocampal fimbria-fornix. In all cases, the interaction was attributable to a drop in FA from the first to the second DTI session followed by a return in FA to baseline levels between the second and third DTI session, observed in the ethanol but not the dextrose control group. For MD, the ethanol effects, identified as group-by-session interactions, were limited to the hippocampal fimbria-fornix: left ($F(2,32) = 6.179$, $p = 0.0054$); right ($F(2,32) = 10.917$, $p = 0.0002$). The interaction indicated a rise in MD at DTI 2 followed by a return to baseline at DTI 3 in the ethanol-treated group only. Proton MRS, acquired as part of the imaging session approximately 5 min before DTI acquisition, provided a measure of acute brain alcohol levels (BrAL). To determine whether the effects on DTI metrics were due to presence of brain ethanol, relations between BrALs and DTI metrics were evaluated. There were no significant correlations between BrALs and FA. Although the correlations between BrALs and MD were not significant for any region, there were trends for lower MD with higher ethanol for the hippocampal fimbria-fornix (right: Rho = -.46, $p = 0.174$, left: Rho = -0.33, $p = 0.347$). Relations between average BALs attained during the 4-day binge and DTI metrics were similarly evaluated. Genu and splenium correlations were not significant. By contrast, for the hippocampal fimbria-fornix, higher BALs correlated modestly with lower FA (right: Rho = -0.86, $p = 0.029$, left: Rho = -0.58, $p = 0.082$) and higher MD (right: Rho = 0.49, $p = 0.150$, left: Rho = 0. = 0.42, $p = 0.229$). This effect was opposite to the trends for BrALs at the time of scanning. Together, these correlations suggest a different effect of the 4-day exposure from the acute presence of alcohol. *Chronic vapor experiment*. In contrast with the effects of binge EtOH exposure, chronic ethanol via vapor chamber failed to demonstrate effects on either FA or MD in any fiber track quantified at either the 16- or 24- week examination. The lack of effect on regional DTI metrics at either post-EtOH exposure time was in spite of similar average BAL and BrALs achieved in both studies at DTI 2.

Conclusions: The acute binge model produced reversible changes in white matter microstructural integrity in the genu and hippocampal fimbria-fornix but not the splenium. That the chronic exposure model did not show exposure effects in the regions measured, although it has previously been shown to produce ventricular and brain neurochemical changes, suggests neuroadaptation of white matter microstructure to chronic ethanol exposure.

Keywords: magnetic resonance imaging, animal models, white matter, in vivo, neuroadaptation

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

M171. Differentiating Neural Networks Underlying Risk for Depression in Youth

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Background: Major Depressive (MDD) and Bipolar Disorders (BD) are among the most prevalent of psychiatric disorders, and the strongest risk factor for either MDD or BD is a family history of the disorder. However, we know relatively little about the mechanisms by which offspring of parents with mood disorders are placed at elevated risk for these disorders. Further, the behavioral manifestations of MDD and BD have been well described but in their depressive states, these two disorders can present similarly leading to misdiagnosis and improper treatment. This is an important impetus for elucidating reliable biological factors that can distinguish these disorders, and predict who goes on to developing them. One way to elucidate mechanisms that might underlie risk for developing these mood disorders is to use magnetic resonance imaging (MRI) technology to assess in vivo structural and functional brain abnormalities among youth at risk for MDD (MDDrisk), youth at risk for BD (BDrisk), and healthy controls without any familial risk for mood disorders (HC). Specific differences in an at-risk population may suggest intrinsic deficits that precede the onset of observable illness versus being a consequence of illness burden. In addition, examining youth at risk for MDD and BD permits the evaluation of neurobiological factors associated with risk for progression to mood syndromes independent of common illness associated confounds including comorbidities, medication exposure, or substance use. In this study, we aimed to compare neural circuit structural and functional abnormalities among healthy offspring of parents with MDD, healthy offspring of parents with BD, and healthy controls.

Methods: Using voxel-based morphometry, we analyzed average gray matter volumes of 96 girls (30 MDDrisk, 16 BDrisk, and 50 HC) between the ages of 8–15 years. We also analyzed intrinsic functional connectivity in 56 participants who completed a resting state scan (10 MDDrisk, 17 BDrisk, and 29 HC). Using a hypothesis driven approach, we seeded three brain regions known to be associated with aberrant functional connectivity in individuals with MDD and BD.

Results: MDDrisk youth exhibited a predicted pattern of reduced hippocampal and amygdalar gray matter volumes, while BDrisk youth showed reductions in bilateral putamen but increased volumes in the hippocampus and parahippocampal gyrus (all p's < 0.001) relative to the other two groups. Upon seeding the ventral striatum (including the caudate, putamen, and globus pallidus), MDDrisk youth showed significantly decreased connectivity to the ACC compared to HC ($p < 0.001$). When seeding the medial prefrontal cortex (MPFC), a more clear separation of connectivity patterns was found between MDDrisk and BDrisk youth. Whereas MDDrisk youth showed decreased connectivity between the MPFC and amygdala, BDrisk youth showed increased connectivity between these regions ($p < 0.001$). When seeding the subgenual cingulate (sgACC), an important target for deep brain stimulation in treatment refractory depression, BDrisk youth showed decreased functional connectivity to the parietal cortex and increased connectivity to the posterior cingulate, both part of the default mode network (DMN) ($p < 0.001$). This dissociable pattern of decreased connectivity in a more anterior DMN region and increased connectivity in a posterior DMN region is the opposite of what has been observed in MDD.

Conclusions: Results suggest that youth at risk for MDD and BD have deficits in structural integrity in different regions associated with the generation of emotion and motivation even prior to the onset of symptoms. Increased volumes in youth at risk for BD may represent either a lack of pruning or compensatory mechanisms to prevent the onset of mood symptoms. Results from resting state analyses suggest a pattern of deficits in functional connectivity that is both overlapping and distinct between MDDrisk and BDrisk youth, providing a neurobiological explanation for overlapping and distinct clinical phenotypes. We aim to advance our observations of these structural and functional patterns to determine how they can guide future interventions that target these neural circuits.

Keywords: risk, pediatric, mood, amygdala, prefrontal

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M172. Pre-symptomatic Functional Brain Changes in PS1 E280A Mutation Carriers Compared to Other Biomarkers: Pilot Data from the Alzheimer's Prevention Initiative Biomarker Project

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Background: The Alzheimer's Prevention Initiative (API) has conducted pilot biomarker studies to characterize and compare age-related changes in the preclinical course of autosomal dominant Alzheimer's disease (AD) in the *PS1 E280A* mutation kindred from Antioquia, Colombia. We previously presented evidence of changes in florbetapir positron emission tomography (PET) 16 years before (Fleisher *et al*, Lancet Neurology, 2013), cerebrospinal fluid AB42 and Tau 14 years before, and hippocampal volume reductions 7 years prior to the median age of MCI onset (44 year, 95% CI 43–45). We have now completed FDG PET and resting-state functional MRI (rsfMRI) assessments for comparison.

Methods: Fifty-two family members from Colombia received FDG PET measurements on a Siemens Biograph mCT 64 PET CT scanner with 30-min dynamic emission scan acquired 30-min after the IV administration of 5mCi of FDG. The cohort included 12 symptomatic carriers: 7 with MCI (46 years ± 4.5), 5 with AD dementia (51 years ± 1.9), 20 cognitively normal mutation carriers (33 years ± 8.2) and 20 non-carriers(NC, 34 years ± 8.7) between ages 20–56 years old. Regional-to-whole brain cerebral metabolic rates of glucose (CMRgl) were compared between *PS1 E280A* mutation carriers and NC, accounting for age effects. A nonlinear model was used to characterize CMRgl decline and to estimate the age at which its reductions in mutation carriers became apparent as compared to NC. Voxelwise and region of interest analyses were used to compare resting state fMRI default mode network (DMN) between carriers and NC. Comparison of all biomarker trajectories and age of change onset was performed.

Results: Compared to NC, asymptomatic mutation carriers had significantly lower CMRgl most prominently in the posterior cingulate and precuneus regions. Onset of biomarker changes appears to occur in association with *PS1 E280A* autosomal dominant AD in the order of amyloid PET CSF Aβ & Tau FDG PET Hipp volumes. Precuneus CMRgl reductions appear to begin approximately at age 34 years old, approximately 10 years prior to MCI diagnosis in this population. Compared to NC, functional connectivity in asymptomatic/symptomatic carriers was significantly reduced, and age-related connectivity was also reduced in carriers compared than in NC.

Conclusions: Functional PET and MR imaging identifies pre-symptomatic brain changes in *PS1 E280A* carriers. CMRgl reductions are seen about 10 years prior to the median onset of MCI. rsfMRI appears less sensitive to individual age-associated changes, possibly due to high inter-individual variability. These biomarkers provide additional tools for evaluating pre-symptomatic Alzheimer's disease at various stages of pre-symptomatic disease.

Keywords: Alzheimer's disease Amyloid FDG PET MRI biomarkers

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is employed by Gilead, which is not involved in neuroscience or related drugs., Part 2: My wife is employed by Gilead, as noted above. No conflict with this work., Part 3: Scientific advisor to Siemens. , Part 4: No personal compensation. See list of contracts for which I'm PI in answer to question 2, with funding going to my organization.; X. Liu, Nothing to Disclose; W. Lee, Nothing to Disclose.

M173. Multiscale Computer Modeling of Antipsychotic Targets: ER Parameters Modulate Calcium Wave Propagation

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Background: Many of the genes and proteins identified in the pathogenesis of schizophrenia involve alterations in calcium ($Ca2+$) signalling. Some of these alterations are effected via NMDA receptors (NMDAR). NMDAR antagonists worsen symptoms of schizophrenia and, by disinhibiting GABA-ergic neurons, result in heightened activation of pyramidal cell NMDAR, and increased $Ca2+$ influx. Clozapine and haloperidol also block the release of calcium from inositol trisphosphate (IP3) receptors (IP3Rs). $Ca2+$ waves are one hypothesized mechanism allowing for $Ca2+$'s rapid propagation from source to distal targets along primary dendrites. In some cases, where $Ca2+$ waves reach the soma and the nucleus, they influence patterns of gene expression. At least two modes of $Ca2+$ wave spread have been suggested: a continuous mode that depends on continuous underlying substrate that can regenerate the $Ca2+$ wave, presumably based on relative homogeneity of endoplasmic reticulum (ER) within the cell; and a saltatory mode where $Ca2+$ regeneration occurs at discrete points with diffusion between them. Understanding how changes at molecular and cellular levels result in changes in behaviors and symptoms is the goal of multi-scale modeling (MSM). MSM models phenomena across different temporal and spatial scales. In order to understand how variations of multiple components at the molecular and subcellular levels affect $Ca2+$ waves, we developed a multiscale, reaction-diffusion computer model of an apical dendrite.
Methods: Simulations were performed using NEURON (www.neuron.yale.edu). We used our model to test both modes of $Ca2+$ wave spread. The model included diffusible IP3, diffusible $Ca2+$, IP3Rs, ER $Ca2+$ leak, and ER pump (SERCA) on ER. $Ca2+$ is released from ER stores via IP3Rs in response to binding of both IP3 and $Ca2+$. This results in $Ca2+$-induced $Ca2+$ release (CICR), which increases the efficiency of spread of $Ca2+$ waves. SERCA pumps $Ca2+$ back into the ER. We adjusted the parameters in order to replicate $Ca2+$ wave initiation and rate of spread observed in vitro. In order to explore similarities and differences between the continuous and saltatory modes, we compared the effects of 3 patterns of hypothesized IP3R distribution: 1. continuous homogeneous ER, 2. areas of increased ER density (ER stacks, so called since they involve folia of stacked ER); 3. hotspots with increased IP3R density (IP3R hotspots).
Results: All 3 models could produce spread of $Ca2+$ waves at a velocity similar to that measured experimentally ($\sim$50 m /sec). However, sensitivity to differences in ER density differed greatly across the 3 patterns. Continuous ER showed far greater sensitivity to IP3R density increase than did the other patterns: time to onset was reduced from 80 to 10 ms, speed increased from 30 to 80 m/sec, duration at one location increased from 0.8 to 1.1 s. Increases in SERCA density resulted in opposite effects: time to onset decreased from 10 to 40 ms, speed decreased from 60 to 35 m/sec, and duration was reduced from 1.2 to 0.6 s. By contrast, our measures were generally insensitive to changes in density of IP3R hotspots or stacks, although time to onset showed a reduction in both cases from 10 to 5 ms. We also tested the effects of varying distance between hotspots between 10 and 100 m. Speed decreased from 75 to 55 m/sec with increasing distance between hotspots, with other measures insensitive to this distance variation.
Conclusions: Our modeling shows that alterations in IP3R or SERCA functioning modulates $Ca2+$ wave propagation and predicts that in vivo IP3R hotspots are more effective in boosting signals, relative to ER stacks. Clinically, $Ca2+$ wave modulation suggests that reduction of calcium-induced hyperexcitability resulting from antipsychotic blockage of IP3Rs could be one way in which antipsychotics alter schizophrenia pathophysiology. Antipsychotics modulate multiple molecular targets, and produce multiple changes at the level of behavior, thoughts and emotions. We will only be able to trace the complex fan-out and fan-in of effects by modeling across temporal and spatial scales from the nanoscale of molecules to the millisecond/micron scale of neurons to the centimeter/second scale of large ensembles and up to behavior and behavioral dysfunction. MSM can provide a tool to explore the complex dynamic interactions occurring in the pathogenesis and treatment of complex mental disorders such as schizophrenia.
Keywords: multiscale modeling - calcium wave - psychosis - antipsychotics - computer model
Disclosures: M. Sherif, Nothing to Disclose; R. McDougal, Nothing to Disclose; S. Neymotin, Nothing to Disclose; M. Hines, Nothing to Disclose; W. Lytton, Nothing to Disclose.

M174. Association of Clinical Variables and Calf Arterial Compliance in Veterans with Psychiatric Diagnoses

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Background: Peripheral arterial compliance (PAC) is a measure of elasticity of the arteries. Low PAC is associated with arteriosclerosis, stroke, and myocardial infarction. In 376 subjects who received diagnostic coronary angiography PAC was significantly associated with coronary stenosis. Prior work from our group found that PAC was lower in Veterans Affairs (VA) psychiatric patients than nonpsychiatric controls and that treatment withquetiapine and

risperidone was associated with reduced PAC compared to controls. We now examine clinical variables as potential predictors of reduced PAC.
Methods: Seventy five male psychiatric patients were enrolled at the Atlanta VA Medical Center in a cross-sectional study. Subjects were 18–70 years old (mean ± SD 53.5 ± 8.6). Forty eight were currently treated with an antipsychotic medication; 28 were off antispychotics for at least two months. Exclusion criteria were: diabetes mellitus, weight >300 lbs, triglyceride (TG) >600 mg/dl, current clozapine treatment, a history of myocardial infarction or unstable angina within the past six-months, diagnosis of HIV/AIDS or collagen vascular disease, substance (except nicotine or caffeine) and/or alcohol dependence within three-months of testing. Compliance was measured with a computerized plethysmography device (vasogram, Vasocor, Inc.). Linear regressions with dependent variables of log (calf compliance) included the following independent variables: age, race, number of factors of the metabolic syndrome, body mass index (BMI) entered in the models as BMI and BMI squared to allow for a curvilinear association between BMI and calf compliance), current treatment with a statin, diagnosis of schizophrenia or schizoaffective disorder, and current antipsychotic treatment.
Results: Among 75 subjects, 40 were Caucasian, 19 were on a statin, 48 were on an antipsychotic, and 28 were diagnosed with schizophrenia/schizoaffective disorder. Age ($p<0.76$), smoking ($p<0.53$), treatment with a statin ($p<0.64$) and a diagnosis of schizophrenia/schizoaffective disorder ($p<0.84$) were not significant predictors of calf compliance and were dropped from the model. The reduced model containing number of metabolic syndrome factors, BMI, BMI squared, race, and use of antipsychotic medication was significant, with an omnibus $p<0.0003$ predicting 28% of the variance in log (calf compliance). Caucasians had higher log calf compliance than African Americans ($p<0.02$). Subjects on an antipsychotic had a significantly lower log calf compliance than those who were not on an antipsychotic ($p<0.03$). BMI had a significant inverted 'U' shaped association with compliance. Compliance increased as BMI increased to a BMI of 35 kg/m^2 and decreased thereafter. No model was a significant predictor of thigh compliance.
Conclusions: In this small sample, race, BMI, and treatment with an antipsychotic were significant predictors of calf compliance. Other variables such as age, smoking, diagnosis of schizophrenia or schizoaffective disorder, and treatment with a statin were not significant predictors of calf compliance. Obesity and the metabolic syndrome are common in people with psychiatric diagnoses, and antipsychotic treatment may worsen these morbidities. We previously reported that PAC is low in people with psychiatric diagnoses, even if they are not currently treated with antipsychotics. Measuring PAC is a novel non-invasive way to follow cardiovascular risk in psychiatric patients. Future studies are warranted to better understand the pathophysiology of arterial compliance in psychiatric patients. Funding: VA Merit Review grant (PI: Erica Duncan). The Mental Health, Research and Development, and Health Services Research & Development Service Lines of the Atlanta Veterans Affairs Medical Center contributed infrastructure support (PI: Erica Duncan, MD). Sorkin: NIDDK P30 DK072488 (NORC), NIA P30 AG028747 (Pepper Center), and the Baltimore VA Geriatrics Research, Education, and Clinical Center.
Keywords: Calf Arterial Compliance, Male Veterans, Psychiatric Diagnoses, Cardiovascular risk, Metabolic syndrome, antipsychotics.
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M175. High Variability and Lack of Change on the ADAS-Cog: Placebo Analyses of the CODR Database

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Background: The Alzheimer's Disease Assessment Scale-Cognitive Section (ADAS-Cog) is the most commonly used primary neurocognitive endpoint in clinical trials of mild-moderate Alzheimer's disease. However, concerns have been raised regarding the lack of sensitivity of this instrument in mild disease and with respect to the magnitude of error variance. In an effort to drive advances in Alzheimer's disease therapeutic development, the Critical Path (C-Path) initiative created the C-Path Online Data Repository (CODR) that contains data from the placebo arms of over 20 clinical trials. We analyzed the CODR database to explore change in the ADAS-Cog as a function of time and baseline MMSE score, to further inform clinical trial design for this population.
Methods: There are a total of 24 studies in the CODR database. We eliminated trials of less than 6 months duration (n = 2), open label extension studies (n = 2) and trials that did not include the ADAS-Cog as an endpoint (n = 6). There were 14 studies remaining, with a total of 3,939 subjects across 26,123 visits. We analyzed overall ADAS-Cog visit-to-visit change scores for visits 90 days apart to quantify variability. Change scores over time were analyzed as baseline to 6-month change, baseline to 12-month change, and baseline to 18-month change. Change scores over time were also analyzed as a function of baseline MMSE score.
Results: Mean ADAS-Cog scores at baseline ranged from 9.3 (± 5.2 SD) to 27.8 (± 9.6 SD). The visit-to-visit test-retest correlation for the ADAS-Cog was .91. Average visit-to-visit change on the ADAS-Cog was .5 (± 5.2) ranging from -35 to 40; 40% of subjects improved during the 90-day visit window. Average change from baseline was 1.0 (± 5.7), 2.8 (± 7.1), and 4.0 (± 8.1) for 6-, 12- and 18 months, respectively; 42%, 34% and 32% of subjects improved, respectively. MMSE was a significant predictor of change in ADAS-Cog score from baseline to 6-, 12-, and 18 months ($\beta = -0.18, = -0.22$, and $= -0.27$, all p's $< .05$) with higher baseline MMSE scores associated with less decline over time.
Conclusions: Large variability and extreme outliers in visit-to-visit ADAS-Cog change scores, including those of a biologically implausible magnitude, were fairly common,

suggesting significant error variance. Overall change on the ADAS-Cog over time was somewhat less than expected based upon published data. This may therefore reflect a publication bias whereby failed trials are less likely to be reported in the peer-reviewed literature. Change on the ADAS-Cog was strongly dependent upon baseline MMSE, and visit-to-visit variability on the ADAS-Cog was fairly high. These findings suggest that accurate subject selection is critical for obtaining placebo decline on the ADAS-Cog, and that in-study quality control methodologies should be further explored for efficacy in reducing error variance.
Keywords: Alzheimer's disease, Dementia, Placebo Response, Clinical Trials, Methodology
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M176. Comparative Trials of Long-Acting Injectable vs. Daily Oral Antipsychotic Treatment in Schizophrenia: Do Pragmatic vs. Explanatory Study Designs Matter?

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Background: Potential advantages of long-acting injectable (LAI) antipsychotic (AP) treatment over daily oral AP agents in patients with schizophrenia lie in theoretical advantages associated with removing the need for daily adherence. However, findings from comparative studies of LAI treatment versus oral AP agents are inconsistent. This may be partly due to differences in the study design characteristics (ie, pragmatic versus explanatory, patient selection, sample size, analytic approaches, etc.). Pragmatic (or effectiveness) studies seek to answer whether an intervention works under usual or real-world conditions, whereas, explanatory (or efficacy) studies ask whether an intervention works and is efficacious and/or safe in an absolute sense for the population being studied. It is often difficult for explanatory trials to address issues related to adherence due to requirements for highly-controlled and well-defined treatment conditions that are necessary to address the primary questions for which this type of trial is designed. These often deviate significantly from conditions found in real-world treatment settings. We rated the pragmatic:explanatory nature of injectable LAI versus oral AP agent comparative trials and related these to the study conclusions.
Methods: A literature search identified direct comparative, parallel-arm studies of LAI treatment versus oral AP agents in schizophrenia with $\geqslant$100 subjects published between January 1993 and July 2013. Excluded were pharmacokinetic or dose-finding studies. In addition, a manual review of references in recent meta-analyses on this topic (Kirson *et al*, 2013; Kishimoto *et al*, 2013; Leucht *et al*, 2011; Fusar-Poli *et al*, 2012) was performed to identify any additional published studies. A total of 12 studies were identified (listed by most recent publication year): (1) Bitter *et al*, 2013; (2) Grimaldi-Bensouda *et al*, 2012; (3) Tiihonen *et al*, 2011; (4) Rosenheck *et al*, 2011; (5) Gaebel *et al*, 2010; (6) Kane *et al*, 2010; (7) Macfadden *et al*, 2010; (8) Olivares *et al*, 2009; (9) Zhu *et al*, 2008; 10) Keks *et al*, 2007; 11) Tiihonen *et al*, 2006; and 12) Tavcar *et al*, 2000. ASPECT-R (A Study Pragmatic: Explanatory Characterization Tool-Rating [Bossie *et al*, 2012]) was used to rate the pragmatic:explanatory nature of each study's design on 6 domains: participant selection, intervention flexibility, medical practice setting/practitioner expertise, follow-up intensity/duration, primary trial outcomes, and participant compliance. Domain ratings are: 0 = extremely explanatory, 1 = very explanatory, 2 = explanatory, 3 = elements of both, 4 = pragmatic, 5 = very pragmatic, 6 = extremely pragmatic. The 12 studies were rated by author (CB and LA) consensus with ASPECT-R.
Results: For 6 of the studies, all domains were rated as more pragmatic and all concluded an advantage for LAI treatment versus oral AP agents (Bitter *et al*, 2013; Tiihonen *et al*, 2011; Olivares *et al*, 2009; Zhu *et al*, 2008; Tiihonen *et al*, 2006; and Tavcar *et al*, 2000). For one study, most domains were rated as more pragmatic and it concluded an advantage for an LAI versus oral AP agents (Grimaldi-Bensouda *et al*, 2012). Two studies were rated as having both pragmatic/explanatory design elements; with one of these studies (Rosenheck *et al*, 2011) concluding no advantage for an LAI versus oral AP agents, and the other (Gaebel *et al*, 2010) concluding an advantage. For 3 studies, most domains were rated as more explanatory; they concluded no advantage for an LAI versus oral AP agents (Kane *et al*, 2010; Macfadden *et al*, 2010; Keks *et al*, 2007).
Conclusions: Categorization of study designs comparing LAI treatment versus oral AP agents by whether they were predominately explanatory or pragmatic suggests that those with more pragmatic designs demonstrate outcome advantages for LAI treatment. Explanatory designs may introduce features that obscure potential differences. Other unidentified factors may also influence outcomes. Confirmation by independent raters with ASPECT-R is needed.
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Keywords: ASPECT-R, pragmatic, explanatory, outcomes, long-acting injectable
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M177. Mapping of the Brain-wide of the Glymphatic Waste Removal Pathway by MRI and PET Imaging

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Background: Clearance of interstitial waste products is essential to normal brain function, and disturbances in waste removal of toxic products such as amyloid beta and tau proteins are implicated in evolving Alzheimer's disease pathology (1,2). In most body organs lymphatic vessels are essential for drainage of exudates (waste proteins and solutes), however, the brain is unique in this regard because it lacks a conventional lymphatic drainage system. We have identified a novel, brain-wide pathway of cerebrospinal and interstitial fluid exchange and transport—designated 'the glymphatic system' - consisting of (1) a para-arterial inflow path, (2) a trans-astroglial exchange system, and (3) a paravenous outflow path that effectively flushes metabolic waste products from the brain (3,4). We started developing clinically relevant imaging approaches to quantify glymphatic pathway function in the live mammalian brain. Here we present novel data demonstrating that the glymphatic pathway activity can be quantified and compared across groups or over time in rodent as well as non-human primate brain by magnetic resonance imaging (MRI) and positron emission tomography (PET).
Methods: Under anesthesia, Sprague-Dawley rats underwent lumbar intrathecal injection of paramagnetic contrast (Gd-DTPA) and dynamic, T1-weighted magnetic resonance imaging (MRI) of the brain. K-means cluster analysis were applied to the dynamic contrast-enhanced MRIs to characterize kinetic patterns (contrast influx/efflux time-domains) of the glymphatic pathway. In a separate series of rats we also tested the feasibility of using combined PET-MRI and intrathecal administration of Gd-DTPA as well as [^{18}F]fluoride to visualize the glymphatic transport system in the rodent brain. Finally, given the potential clinical translation of these studies to humans, we also executed dynamic PET studies to test the hypothesis that [^{18}F]fluoride is transported via the glymphatic pathway in the non-human primate brain similarly to that observed in the rodent brain.
Results: In the rodent brain, cluster analysis of MRIs identified three different types of glymphatic pathway transport: (1) rapid,para-arterial influx, (2) parenchymal exchange and (3) slower exchange and clearance. Further, by applying cluster analysis to the early (0–30 min) or late ($>$2hr) time frames it was possible to quantify tissue associated only with glymphatic pathway influx and efflux, respectively. Anatomically, key influx nodes included the optical chiasm, pineal gland, pons and hippocampus. The combined PET-MRI experiments in rodent brain provided proof-of-principle that Gd-DTPA and ^{18}F follow the same glymphatic transport conduits. Finally, preliminary observations in two non-human primates (baboon) receiving intrathecal ^{18}F and undergoing dynamic PET imaging of the brain over 4 h revealed influx and clearance routes of the glymphatic pathway similar to that observed in the rodent brain.
Conclusions: Our data shows that simple inflow and efflux parameters of convective CSF/ISF fluxes via the brain-wide glymphatic pathway can be obtained using MRI and PET in both rat and NHP brains after intrathecal delivery of contrast agents and/or radiolabeled tracers, and this glymphatic activity can be quantified and compared across groups or over time. The PET approach might be advantageous from the point of view of higher sensitivity of PET in comparison to MRI and the imminent ability to perform simultaneous PET-MRI with the technological advancement in hybrid scanners for clinical use. The data presented constitute, to our knowledge, the first attempt to develop a clinical diagnostic test to quantify glymphatic pathway function and in the future identify patients at risk for developing AD. Moreover, our hope is that these studies will facilitate identification of targets for slowing or even reversing amyloid deposition by improving glymphatic clearance.
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M178. Developing a Smart Phone App to Monitor Mood, Social Rhythms, Sleep and Social Activity: Technology to Support Effective Management of Bipolar Disorder

Ellen Frank*, Mark Matthews, Tanzeem Choudhury, Stephen Voida, Saeed Abdullah

Background: Serious mental illnesses, including bipolar disorders (BD), account for a large share of the worldwide healthcare burden—estimated at $62.7B in the U.S. alone. BD is a family of common, lifelong illnesses associated with poor functional and clinical outcomes, high suicide rates, and huge societal costs. Interpersonal and Social Rhythm Therapy (IPSRT), a validated treatment for BD, helps patients lead lives characterized by greater stability of daily rhythms, using a 5-item paper-and-pencil self-monitoring instrument called the Social Rhythm Metric (SRM). IPSRT has been shown to improve patient outcomes; however, maintaining adherence to self-monitoring remains a major challenge in implementing the treatment.
Methods: As part of the MoodRhythm development program, we sought to create a system combining

smartphone-based self-report with robust, privacy-sensitive, and automated sensing to help patients maintain stable social rhythms and moods. Specifically, in the development of the MoodRhythm app we aimed to:
design interaction techniques that help patients to *assess* and *reflect* on trends or changes in their daily rhythms, social interactions, and mood and *motivate* them to incorporate the system into their self-care;
remind patients to engage with the system on a daily basis, *augment* the data traditionally collected through patient journaling, and *reduce the burden* of self-report while dramatically *enhancing the validity* of the data collected; and
explore mechanisms for *connecting* smartphone data with other health data systems as part of ongoing treatment and a means for alerting clinicians when significant changes in a patient's mood or behavior are detected.
Results: Our current prototype for MoodRhythm is able to use the phone's onboard sensors to automatically track sleep and social activity patterns. It is also facilitates patient self-report of the 5 SRM items, as well as the creation of tailored items and provides reminders to complete them. Initial feedback from experienced IPSRT clinicians and from a small group of patients with whom MoodRhythm has been tested has been uniformly positive.
Conclusions: The next steps in the MoodRhythm design process include: (1) running *participatory design workshops* involving focus groups of members of local BD support groups, researchers, and clinicians to identify improvements to the prototype and articulate new scenarios of use; (2) creating long-term opportunities for patients and clinicians to serve as co-designers by supporting their use of robust system prototypes on their own devices, allowing us to elicit feedback on an ongoing basis; and (3) formally evaluating the system's effectiveness against existing interventions using the paper-based IPSRT instrument (SRM-5). By empowering patients to more easily monitor social rhythms and interpersonal interactions and giving them tools to motivate long-term adherence and encourage self-reflection on emerging mood and social rhythm trends, MoodRhythm could substantially lower the public health impact of bipolar disorders. Given the fact that circadian regulation is important in a range of disorders including cancer, diabetes and obesity, MoodRhythm has broad potential for improvement of public health.
Keywords: smartphone app; bipolar disorder; self-monitoring
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M179. Cognitive-affective Remediation Training Intervention in Anxiety and Depression

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Background: Anxiety and mood disorders are highly prevalent and difficult to treat. Emerging neurobiological models and the presence of uncontrollable negative emotion suggest a core deficit in cognitive regulation and affective reactivity in both disorders. Here we report the results of a randomized controlled clinical trial among patients with comorbid generalized anxiety and major depressive disorders ($n = 31$) where we used neuroplasticity-based program of adaptive computer exercises or active control.
Methods: The active arm completed a set of cognitive-affective training exercisers that (1) improve cognitive functions by enhancing executive functioning more generally (e.g. working memory, task switching, interference resistance) and (2) improve affective functioning by reducing affective reactivity in general through training positivity bias and emotion labeling. Control group participants completed engaging but non-therapeutic computerized exercises for the same amount of time. Patients completed behavioral assessments of cognitive and affective functioning, and reported on their symptoms before and 3-months after training. In addition, a subset of the participants ($n = 22$) were scanned before and after training on imaging probes of affective functions.
Results: Results showed that participants in the training group showed improvements in executive function (trails B and Go/NoGo performance) and affective functions (recognition of facial expressions). Imaging results indicated reduced amygdala activation during emotional conflict and reduced connectivity within the salience network post-training in the training group. Training-related improvements on executive function exercises were related to lower anxiety and depression symptoms 3-months post-training.
Conclusions: Collectively these results establish that our computerized cognitive-affective training intervention improves dysfunctional neural systems that in turn relate to improved symptom and functioning.
Keywords: cognitive-affective remediation, anxiety, depression
Disclosures: A. Gyurak, Nothing to Disclose; J. Gross, Nothing to Disclose; L. Chan, Nothing to Disclose; A. Etkin, Nothing to Disclose.

M180. DREADDs in Drosophila: Pharmacogenetic Control of Neurons and Behavior in the Fly

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Background: *Drosophila melanogaster* is an important genetic model system that has provided much information on the molecular basis of behaviors conserved with mammalian systems and psychiatric disorders. These include sleep, aggression, social interaction, learning and memory, and response to drugs of abuse that are all mediated by similar and fundamentally shared mechanisms involving neurotransmitters like serotonin, dopamine, glutamate, and GABA. One of the advantages of the fly is the extensive toolkit of genetic methods to manipulate gene expression in the fly. In combination with the ability to precisely control temporal and spatial expression in the fly, there are several methods used to conditionally control

neuronal activity that include temperature sensitive blockade of synaptic vesicle recycling with *shibire*^{ts}, constitutive activation/inactivation with NaChBac/Kir channels, temperature regulated activation/inactivation with TrpA/TrpM channels, and light regulated channelrhodopsins. A disadvantage to these methods is that they each are all essentially switches, and either turn the neuron all on or all off, and have little to no dose responsive control. We have now adapted Designer Receptors Exclusively Activated by Designer Drugs (DREADD) technology to the fruit fly to provide true dose responsive control of neuronal function and behavior through manipulation of GPCR receptors and downstream effector pathways. Unlike these other methods, additional equipment like dedicated temperature incubators or blue light sources and fiber optics are not required, activating drug is simply fed to the fly. Furthermore, conditional control of activity is reversible. Due to the ubiquitous nature of GPCRs, this system will also be useful in the examination of the role of signal transduction pathway effectors in almost every tissue of the fly, and is not limited to study of only neurons and behaviors.
Methods: UAS-DREADD constructs were created for each of the three primary mammalian muscarinic DREADDs (hM4Di, a silencing receptor coupled to Gi; hM1Dq, an activating receptor coupled to Gq; rM3DBs, coupled to Gs and increases in cAMP levels), and transgenic fly strains created for each. DREADDs were expressed in discreet neuronal circuits and tissues using various GAL4 drivers and the ability of activation of the DREADDs to control behaviors was examined in a panel of behaviors that included sensory perception, learning and memory, circadian, and courtship. Effector pathway responses were measured in tissue culture. Neuronal activity was measured by real-time live cell calcium imaging in larval brain ventral ganglia neurons using GcAMP and confocal microscopy. Heart rate control was measured using larval heart preparations and light microscopy. The activating ligand clozapine-N-oxide (CNO) was administered by feeding to flies in the food, or application in media.
Results: DREADD activation was found to dose responsively and reversible control behaviors, neuronal activity, and physiological processes by simple feeding or application of activating ligand, CNO.
Conclusions: We have successfully translated DREADD technology from mammalian systems to *Drosophila*. DREADD activation confers dose responsive and reversible control over not only signal transduction and effector pathways, but also neuronal activity, behaviors, and physiological processes. DREADDs provide an additional level of more fine control of neurons and circuits than the current switch-based all on or all off approaches. This control to only partially activate or inactivate a neuron acutely or chronically allows us to study more subtle behaviors that may be masked by more aggressive methods. In our previous work, we generated several genetic tools for examination of the *Drosophila* serotonin system, and defined a role for serotonin in many behaviors relevant to neuropsychiatric disorders like social interaction and learning and memory. We are now incorporating DREADD technology into our study of serotonin neuropharmacology in the fly to enhance our discovery of conserved mechanisms underlying behaviors that will ultimately enhance our understanding of human psychiatric diseases.
Keywords: Genetic model system, learning and memory, courtship, sensory perception, fruit fly
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M181. Forecasting Non-remitting PTSD Symptom Trajectory by Advanced Modeling Methods

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Background: Predicting pathways to chronic PTSD has significant clinical and public health implications but current risk indicators are inconsistent and limited. Previously identified in a large cohort of recent trauma survivors ($n = 957$) using Latent Growth Mixture Modeling, trajectories of PTSD symptoms from one-week to fifteen-months, include Rapid Remission (56%), Slow Remission (27%), and Non-Remission (17%), the non-remission class comprising the majority PTSD cases at fifteen months, and not responding to cognitive behavioral therapy (CBT). Innovative approaches to forecasting membership in a non-remitting, treatment resistant class may improve our ability to identify, shortly after trauma exposure, survivors at high risk of developing PTSD. We tested the robustness of seven machine learning forecasting methods to predicting the non-remitting class from predictor variables collected during the days that followed trauma exposure.
Methods: Consecutive trauma survivors admitted to a general hospital emergency department were screened and followed longitudinally and $n = 125$ with Acute PTSD received efficient cognitive behavioral therapy within a month of the traumatic event. CBT was equally distributed among trajectory classes. Survivors were followed regardless and blindly of their participation in treatment. Markov boundary feature selection was used to identify a parsimonious set of trajectory predictors from 68 candidate variables. That set was than used to compare seven classification algorithms [two variants of linear Support Vector Machines (SVMs), polynomial SVMs, AdaBoost, Random Forests, Bayesian Logistic Regression (BBR) and Kernal Ridge Regression (KRR)] for their ability to build accurate multivariate classification models separating non-remission from other trajectories: Support Vector Machines (SVMs), two Optimized SVMs, AdaBoost, Random Forests, Bayesian Logistic Regression (BBR) and Kernel Ridge Regression (KRR).
Results: Variables selected by Markov boundary method robustly predicted PTSD symptom course yielding with mean area under receiver operating characteristics curve (AUC) across 100 cross-validation runs ranging from 0.77–0.80. The seven machine learning classification methods

worked equivalently well: Linear SVMs AUC = 0.78, 95% CI: [0.74 0.82]; Linear Optimized SVMs = 0.78, 95% CI: [0.73 0.82]; Polynomial Optimized SVMs = 0.77, 95% CI: [0.73 0.81]; Random Forests = 0.80, 95% CI: [0.76 0.84]; AdaBoost = 0.79, 95% CI: [0.75 0.83]; KRR = 0.79, 95% CI: [0.75 0.83]; BBR = 0.78, 95% CI: [0.74 0.82]. Predictors that identified in >90% of cross validation training sets included specific demographic (age), trauma characteristics (exposure to terror, head injury) emergency room parameters (pain levels, time in the emergency room) formal symptoms (total PTSD and Acute Stress Disorder severity and, independently, difficulty concentrating, nightmares, flashbacks, de-realization), depression, sense of worthlessness, and subjective perception indicators (participants' and clinicians' Clinical Global Impression, perceived need of help, perceived social support). Forecasting from PTSD/and ASD symptoms alone performed less well than the previous, unrestricted, array of predictors (AUC = 0.69).

Conclusions: Uncovering the heterogeneous course of PTSD symptom during the year that follows a traumatic event provides a predictable non-remitting phenotype with relevance for early detection and treatment. Machine-learning approaches offer a promising way to identify non-remission from readily available features of the immediate response to traumatic events.

Keywords: Post-traumatic Stress Disorder, Early Detection and Prediction, Machine Learning

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M183. Olfactory Identification Deficits Predict Response to Cholinesterase Inhibitors in Patients with Mild Cognitive Impairment

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Background: Odor identification deficits occur early in the course of Alzheimer's disease (AD) and strongly predict the transition from mild cognitive impairment (MCI) to a clinical diagnosis of AD. The olfactory bulb and tract are among the earliest brain structures to show the neuropathological features of AD, and these olfactory regions are rich in acetylcholine. Cholinesterase inhibitors increase the availability of acetylcholine in the brain and show efficacy to a small degree in AD. Several cholinesterase inhibitors (donepezil, rivastigmine, galantamine, and previously tacrine) are FDA-approved for the treatment of AD. In a British pilot study of 25 patients, improvement in odor identification test performance correlated significantly with concurrent global clinical improvement during 3 months of treatment with donepezil. In a sample of patients with MCI, we examined whether odor identification deficits at baseline would predict the likelihood of cognitive improvement during treatment with cholinesterase inhibitors during follow-up.

Methods: At the New York State Psychiatric Institute/Columbia University Memory Disorders Center, 148 patients with mild cognitive impairment were recruited and followed naturalistically at 6-month intervals for up to 9 years. Baseline olfactory identification testing was conducted with the 40-item, multiple-choice format, University of Pennsylvania Smell Identification Test (UPSIT). During follow-up, patients received open treatment with cholinesterase inhibitors based on the study doctor's choice. The outcome measure was the change in episodic verbal memory performance on the 12-item, 6-trial Selective Reminding Test (SRT) from the visit that a cholinesterase inhibitor was initiated to the visit that occurred 12 months later. Only patients who stayed on the cholinesterase inhibitor during these 12 months were included in the analyses.

Results: Nearly all patients who received cholinesterase inhibitors were prescribed donepezil. Lower baseline UPSIT scores were associated strongly with the increase in SRT total recall over 12 months in MCI patients who received a cholinesterase inhibitor ($n = 24$, $r = 0.52$, $p = 0.009$). Lower baseline UPSIT scores were also associated with the increase in SRT total recall in the subset of patients who received cholinesterase inhibitors and were given a subsequent clinical diagnosis of AD ($n = 16$, $r = 0.51$, $p = 0.04$). In regression analyses on the increase in SRT total recall over 12 months, low baseline UPSIT but not baseline SRT total recall predicted improvement in SRT total recall over 12 months of cholinesterase inhibitor treatment. Age, sex and education were not significant covariates in the analyses for the total sample and in the subset that transitioned over time from MCI to a clinical diagnosis of AD.

Conclusions: No clinical predictor or biomarker has been shown consistently to predict response to cholinesterase inhibtors; MRI hippocampal volume and FDG PET have shown equivocal results. Amyloid imaging and CSF biomarkers have not been studied in relation to response to cholinesterase inhibitors. An odor identification test is inexpensive and easy to administer compared to MRI/PET imaging and lumbar puncture for CSF. Odor identification deficits predict long-term improvement with cholinesterase inhibitor treatment. Cholinesterase inhibitors are prescribed widely in patients with AD and a large proportion of patients with MCI also receive this class of medication. Accurate prediction of who should receive cholinesterase inhibitor treatment improves potential benefit while decreasing the risk of side effects without needless drug exposure in patients without AD brain pathology as identified by odor identification deficits. The study findings show that odor identification testing needs to be developed further as a predictor of cognitive improvement with cholinesterase inhibitor treatment, to personalize selection for treatment that may delay clinical conversion to AD, and to select/stratify patients in treatment trials. This strategy can guide treatment by clinicians and have immediate public health impact in these widely prevalent conditions, MCI and AD, where cholinesterase inhibitors are often prescribed.

Keywords: Olfactory identification deficits, Mild cognitive impairment, Cholinesterase inhibitor, Cognitive improvement Personalized treatment

Disclosures: D. Devanand, Nothing to Disclose; G. Pelton, Nothing to Disclose; H. Andrews, Nothing to Disclose; B. Levin, Nothing to Disclose.

M184. ALKS 5461, a Novel Opioid Modulator, Produces Remission and Decreases Core Depressive Symptoms and Anhedonia as an Adjunctive Treatment: A Sequential Parallel Comparison Design Trial in Inadequate Responders to Antidepressants

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Background: Up to two-thirds of patients with major depression do not achieve remission after treatment with currently available antidepressants, all of which rely on direct modulation of monoamine neurotransmitter systems. The use of opiates for depressive syndromes pre-dates the antidepressant era, but is rare in modern practice due to safety concerns related to abuse, physiologic dependence, and respiratory depression. Strategies to optimize opioid receptor and circuitry engagement for depression have received inadequate attention, although the possibility that buprenorphine (BUP) might have potential as a treatment for depression was noted as early as 1982. ALKS 5461 is a novel combination of BUP, a partial mu agonist, and ALKS 33, a potent mu antagonist, co-formulated in fixed ratios and equal doses (BUP mg/ALKS 33 mg). ALKS 5461 is designed to counteract the subjective, rewarding and autonomic effects of BUP while preserving its potential antidepressant properties. ALKS 5461 was studied as adjunctive therapy in subjects having an inadequate response to antidepressants in a recent Phase 2, sequential parallel comparison design (SPCD), randomized controlled trial, conducted in two 4-week stages. Treatment groups included ALKS 5461 2 mg/2 mg (2/2), ALKS 5461 8 mg/8 mg (8/8), and placebo ($N = 142$). All subjects remained on stable doses of SSRI/SNRI therapy throughout the trial. As previously reported, initial analyses found significantly greater improvement for drug *vs* placebo on a range of pre-specified primary and secondary endpoints, including the HAM-D17 total score and response, the MADRS total score and response, and CGI-Severity. ALKS 5461 was generally well tolerated. The most common adverse events were nausea, dizziness, vomiting, sedation, and headache. Additional new analyses were conducted to determine the combined SPCD stage response and remission rates based on MADRS scores, and efficacy outcomes on two core depression symptom scales, the Anhedonia subscale of the MADRS, and the Bech Melancholia scale of the HAM-D17.

Methods: The modified intent-to-treat population (at least 1 dose of randomized drug and at least 1 post-baseline evaluation in each stage) was used to evaluate remission rates, defined as a HAM-D17 score 7 and/or a MADRS total score of 10 after 4 weeks of treatment; improvement *vs* placebo on the Anhedonia subscale of the MADRS (sum of items 1,2,6,7,8); and improvement *vs* placebo on the Bech Melancholia scale of the HAM-D17 (items 1,2,7,8,10 and 13). Data were analyzed for each 4-week stage, and stage-specific estimates were combined using equal weights, using MMRM or tests of proportion differences as appropriate. Stage 2 results represent the enriched sample of re-randomized subjects not responding to placebo in stage 1.

Results: *MADRS response rates:* For stages 1 and 2 combined, differences in responder rates between ALKS 5461 and placebo were -30.3% (2/2, $p < 0.001$) and −20.04% (8/8, $p = 0.028$). *MADRS remission rates*: For stages 1 and 2 combined, differences in remission rates between ALKS 5461 and placebo were −24.5% (2/2, $p = 0.008$) and −13.65% (8/8, $p =$ NS). *Anhedonia subscale of the MADRS:* In the combined stage analysis, change from baseline *vs* placebo was −2.7 (2/2, $p = 0.008$), and −1.2 (8/8, $p =$ NS). *Bech Melancholia scale of the HAM-D17:* In the combined stage analysis, change from baseline *vs* placebo was −1.4 (2/2, $p = 0.021$), and −0.3 (8/8, $p =$ NS).

Conclusions: In a Phase 2 SPCD placebo-controlled trial, treatment with ALKS 5461 was associated with improvements in MADRS response and remission rates, and in exploratory analyses of 2 widely-used, core depression symptom subscales. Both doses of ALKS 5461 showed improvements, with the effects of the 2/2 dose being greater in magnitude and statistically significant in all analyses.

Because the Bech scale captures clinically meaningful core symptoms of depressed mood, guilt, impaired activities, retardation, psychic anxiety and somatic symptoms, the overall study finding is less likely attributed to secondary features of depression. The Anhedonia subscale of the MADRS, composed of the items of apparent and reported sadness, concentration, lassitude, and inability to feel, may capture symptomatology linked to hedonic dysregulation of reward and motivation circuitry and be particularly amenable to opioid receptor modulation.

Consistent with the primary findings, the results of these additional exploratory analyses support further study of ALKS 5461 as a novel and potentially important new adjunctive treatment for this serious, chronic illness.

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Keywords: major depressive disorder, inadequate response to antidepressants, remission, response, anhedonia, melancholia, novel mechanism of action

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M185. MicroRNA Dysregulation in Cerebrospinal Fluid in Patients with Schizophrenia

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Background: Recent studies have linked alterations in microRNA (MiRNA) expression to schizophrenia and other psychiatric disorders. However, most of these studies have used post-mortem brain tissue or whole blood as the source of transcript. By contrast, examination of microRNAs in cerebrospinal fluid (CSF) might provide an *in vivo* biomarker more directly reflecting functional changes in the brain.
Methods: Ten patients with schizophrenia-spectrum disorders and ten healthy volunteers matched to patients in age, sex, and race underwent a lumbar puncture and a blood draw. 15–25 cc of CSF and 5–10 cc of blood were obtained from each subject. Expression of 381 validated microRNAs was assessed from CSF for each of the subjects with the Taqman MicroRNA array (Applied Biosystems). Differential expression analyses were conducted using Significance

Analysis of Microarrays (SAM). MiRNAs found to be significantly dysregulated based on microarray analyses were chosen for validation using qPCR.
Results: The mean age was 43 years (SD = 8.1) in patients and 40 years (SD = 8.8) in healthy controls. Both groups had the same proportion of males (90%) and white subjects (40%). Mean total BPRS score in patients was 30.4 (SD = 5.8). Only miRNAs that were detected in 18 or more (out of 20) CSF or peripheral blood samples were included in SAM analysis. Mean cycle threshold (CT) values for each miRNA were normalized using Mammu6 levels for each subject for each sample. Microarray analysis showed that the mean number of miRNAs detected in CSF was 161.2 in patients and 148.3 in controls. Meanwhile, the mean number of miRNAs detected in peripheral blood was 199.2 for patients and 190.2 for controls. Using a cutoff of $<5\%$ FDR, we found that miR-346 was significantly dysregulated in patients compared to controls (fold change: 5.2, q-value: 0%). Conversely, no miRNAs were significantly different in peripheral blood at FDR levels $<5\%$ between patients and controls. To examine the correlation between miRNA levels in CSF and peripheral blood and to avoid possible confounding factors derived from the presence of psychiatric illness or medication exposure, we compared expression levels of those miRNAs that were expressed in both biofluids in healthy volunteers. At FDR $<5\%$ we found that 61 miRNAs were significantly differentially detected across biofluids. Based on these results and prior relevant literature reports we decided to validate the following miRNAs: miR-346, miR-132, miR-532-3p, miR-532–5p, and miR-660. Results are pending but will be available soon.
Conclusions: A small number of miRNAs are differentially expressed in CSF in schizophrenia patients compared to healthy controls. Additionally, a significant number of miRNAs are differentially detected in CSF compared to peripheral blood, which suggests that CSF may contain a unique miRNA signature. Therefore, the investigation of these miRNAs in CSF may help establish an illness-specific miRNA signature that could help with a better classification and understanding of schizophrenia.
Keywords: MiRNAs, gene expression, cerebrospinal fluid, schizophrenia, psychosis
Disclosures: J. Gallego, Nothing to Disclose; T. Lencz, Nothing to Disclose; B. Cantley, Nothing to Disclose; A. Malhotra, Nothing to Disclose.

M186. Pharmacometabolomics of Atypical Antipsychotics in Bipolar Disorder: An Untargeted Approach

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Background: The use of atypical antipsychotics (AAPs) is becoming a common therapeutic approach in patients with bipolar disorder. However, these medications come with a high risk of metabolic side effects that increase the incidence of metabolic syndrome and cardiovascular disease. Metabolomics, the characterization of all the small molecules in a cell, may begin to elucidate the changes caused by AAPs and allow the identification of candidate metabolic pathways and biomarkers in the treatment and response of patients with bipolar disorder.
Methods: An untargeted metabolomic approach using Liquid Chromatography coupled with Mass Spectrometry (LC-MS) was employed to investigate the metabolite profiles of three groups of patients: (1) Bipolar patients currently taking AAPs (BP-AAP), (2) An age, gender and race matched sample of bipolar patients taking typical antipsychotics or no antipsychotic (BP-NoAAP) and (3) An age, gender and race matched sample of schizophrenia patients taking AAPs (SCZ-AAP). All patients were currently stable and had no changes in their therapeutic regimen for the past 6 months. Univariate and multivariate analyses were performed to identify significant differences between these groups. The study was approved by the University of Michigan Institutional Review Board.
Results: A total of 136 serum samples (83BP-AAP, 33BP-NoAAP and 20 SCZ-AAP) were processed in both LC-MS positive and negative modes with a good range of metabolite coverage. Data was normalized by radiolabeled amino acids added during each sample's run and two significant outliers were removed upon inspection using Principle Component Analysis (PCA). Approximately 325 known metabolites were identified. Paired Least Squared Discriminate Analysis (PLS-DA) showed satisfactory separation using a four component model between the BP-AAP and SCZ-AAP groups. PLS-DA separation was significantly affected by the following metabolites: (1) 1-oleoyl-rac-glycerol (increased in SCZ-AAP), (2) Tiglyl Carnitine (increased in BP-AAP), and (3) Guanosine (increased in BP-AAP). In addition to the above metabolites, leucyl-phenylalanine (increased in SCZ-AAP) was also identified in a Singificance Analysis of Microarray (SAM) approach. Finally, univariate one-way analysis of variance (ANOVA) reinforced the multivariate findings by identifying 1-oleoyl-rac-glycerol and leucyl-phenylalanine as being significantly different ($p = 4.9\text{x}10^{-5}$, FDR = 0.02 and $p < 3.4\text{x}10^{-4}$, FDR = 0.05, respectively) amongst the three groups (in the same directions indicated above).
Conclusions: Our study identified a distinct metabolomic profile in a bipolar population exposed to AAPs when compared to bipolar subjects not taking AAPs and schizophrenia subjects taking AAPs. We identified several metabolites that were significantly influential in creating the distinct metabolomic profiles. Interestingly, 1-oleoyl-rac-glycerol, a glycerophospholipid and by product of cholesterol ester metabolism, was identified as being lowest in the Bipolar group not taking AAPs and highest in schizophrenia subjects taking AAPs. This difference may reflect the overall lower exposure of AAPs in bipolar disorder and therefore, less lipid disruption compared to schizophrenia patients generally having higher exposure to AAPs. Additionally, metabolites involved in purine (guanosine) and essential amino acid (leucyl-phenylalanine) metabolism, as well as lipid catabolism (tiglylcarnitine) were identified as being significantly different amongst the three groups. The preliminary findings of this study require confirmatory identification of each molecule's identity followed by a targeted metabolomics approach in order to make quantifiable comparisons amongst the three groups. Identification of metabolite differences involved in lipid and amino acid pathways are positive findings given the known side effects

of AAPs. With continued exploration, metabolites and genes found within these pathways may prove useful as biomarkers and one day be used by clinicians when employing personalized medicine strategies in bipolar disorder.
Keywords: Atypical, Antipsychotic, Metabolomics, Bipolar Schizophrenia
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M187. Meta-analysis of the Discriminative Validity of Caregiver, Teacher, and Youth Checklists for Assessing Pediatric Bipolar Disorder

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Background: There is tremendous need for validated rating scales to aid in the assessment of pediatric bipolar disorder (PBD). Rates of clinical diagnosis of bipolar disorder have changed markedly over the past two decades (Blader & Carlson, 2007; Moreno *et al*, 2007). Alarmingly, inter-rater agreement between clinicians and semi-structured diagnostic interviews is exceptionally poor about PBD, with an average kappa coefficient of $K = 0.10$ (Rettew *et al*, 2009). Our goal was to meta-analyze all available effect sizes for rating scales and checklists comparing cases with PBD to other youths. Based on prior comparisons of measures within the same sample (Wagner *et al*, 2006; Youngstrom *et al*, 2004; Youngstrom *et al*, 2005), we hypothesized that (a) checklists would significantly discriminate PBD from non-PBD cases, (b) caregiver report would produce significantly larger effects than youth or teacher report, (c) samples using 'distilled' comparison groups—such as health controls or ADHD excluding comorbid mood disorder—would produce significantly larger effects, and (d) caregiver report would continue to show greater validity even after controlling for design features.
Methods: PubMed and PsycINFO searches used the terms (Pediatric OR juvenile OR child* OR adolescen*) AND ('bipolar disorder' OR mani* OR cyclothymi*) AND [(Sensitivity AND Specificity) OR comparison]. Review articles and chapters were checked for additional sources. This generated 764 hits. Inclusion criteria were: presenting sufficient statistics to estimate a standardized effect size comparing scores for cases with PBD (regardless of comorbidity) to other youths. When multiple publications used overlapping samples, the largest sample reporting sufficient statistics was used. Effect sizes were converted to Cohen's *d*, using Hedges' bias correction (*g*) for aggregation and meta-analysis (Hasselbad & Hedges, 1995). Because many studies reported multiple effect sizes, mixed regression models accounted for nesting while also weighting for sample size and within study variance (Lipsey & Wilson, 2001).
Results: We identified 16 distinct samples contributing 59 effect sizes (35 based on caregiver, 10 on youth, and 14 on teacher report; 28 based on unselected clinical comparison groups and 31 based on 'distilled' designs). Across studies, 4652 youth between the ages of 5 and 18 years, of whom 1266 carried research diagnoses of PBD, were included. All samples included parent report; teacher report was available on 1342 of the youths (369 with PBD diagnoses) and youth report was available for 980 cases (300 with PBD diagnoses). Using restricted ML estimation in a mixed regression model, the average effect size was $g = 0.88$, indicating that cases with PBD scored significantly higher than the comparison group. Effect sizes of .8 are considered 'large.' The regression model accounted for 53% of the variance in the effect sizes, Q (3 df) $= 65.38$, $p < 0.00005$. As hypothesized, studies using a 'distilled' comparison group had significantly larger effect sizes, $B = 0.41$, $p = 0.0001$. Teacher report yielded lower effect sizes than caregiver report, $B = -0.78$, $p < .00005$; and youth report also produced lower effect sizes than caregiver report, $B = -0.59$, $p < .00005$. The random effects component was significant after accounting for the three predictors, $v = 0.12$, se(v) $= 0.03$. The regression estimates for a non-distilled sample corresponded to Area Under the Curve estimates of .76 for caregiver report (weighted mean $g = 0.98$), .61 for youth report ($g = 0.39$), and .56 for teacher report ($g = 0.20$), where an AUC of .50 represents chance performance and values greater than .8 are good discrimination.
Conclusions: There is now a large evidence base, several thousand caregiver reports, and a substantial numbers of teacher and youth reports, supporting the use of checklists in the assessment of PBD. Consistent with prior findings comparing multiple instruments within studies (Youngstrom *et al*, 2004; 2005; Wagner *et al*, 2006), caregiver report was significantly better at discriminating cases with PBD from comparison cases than was teacher or youth report. However, whereas youth and teacher report failed to achieve statistical significance in some prior published reports, the improved power and precision of the meta-analyses indicated that all three informants have discriminative validity. Also consistent with prior within-study analyses (Youngstrom *et al*, 2006), design features accounted for significant variance in the discriminative effect size estimates.
Keywords: bipolar disorder, children and adolescents, assessment, meta-analysis, diagnostic efficiency
Disclosures: E. Youngstrom, Part 1: Consultation with Lundbeck; J. Genzlinger, Nothing to Disclose; E. McKinney, Nothing to Disclose; G. Egerton, Nothing to Disclose; A. Van Meter, Nothing to Disclose.

M188. Development of a Lab-on-a-Chip Biosensor for Clozapine Monitoring

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Background: Schizophrenia is a lifelong illness with little recent progress in new pharmacologic treatments. Clozapine (CLZ) is the most effective antipsychotic drug for schizophrenia treatment. Yet, it remains underutilized since

frequent blood draws are required to monitor white blood cell (WBC) counts. In addition, the evidence-based and recommended use of CLZ blood levels to guide treatment response are often underutilized by clinicians. Real-time monitoring of treatment efficacy and safety will enable personalized medicine and better utilization of CLZ. Lab-on-a-chip (LOC) biosensing devices are a promising solution and provide numerous advantages, such as small sample volume, ease of use, fast response, low cost, and high throughput. This could allow on-site testing with immediate results at the point-of-care, such as the pharmacy or physician's office. To date it is unknown if this technology would be accepted and utilized by clinicians and if CLZ detection could be done through a LOC.

Methods: We prepared a survey questionnaire sent to licensed physicians in psychiatric practice in the State of Maryland. This survey asked a series of questions on a 5 point Likert Scale (1 = strongly disagree, 5 = strongly agree) regarding the barriers related to CLZ use, blood draw issues with CLZ, and the physician's interest and willingness to use novel technology and point of care devices to monitor CLZ. In addition, the survey solicited the physician's willingness to increase the utilization of CLZ if LOC technology was available. This survey was sent to approximately 800 physicians in the state of Maryland and response was anonymously returned by mail or Survey Monkey®. In parallel, we have begun development of clozapine detection by a LOC biosensing device. Our approach uses the catechol-modified chitosan redox cycling system, integrated in the LOC, for significant signal amplification through the continuously generated oxidizing current of CLZ acting as a mediator. Our project was to test the ability to detect CLZ in a micro-scale device designed for CLZ monitoring at the point-of-care. Here we present survey data and initial demonstration of clozapine sensing at the micro-scale.

Results: We have received 173 surveys for inclusion into the analysis. Twenty-four percent were age 25–35, 22% were age 36–45, 17% were ages 46–55, 22% were ages 56–65 and 14% were over age 65. Fifty-one percent were male, 67% were White and 25% were residents/fellows. Eighty-six percent had ever prescribed clozapine. Physicians agreed that immediate results of a point of care device would be an improvement over waiting for CLZ blood levels and WBC (3.9 ± 0.9), and both clozapine blood levels and WBC results by point of care would increase the use of clozapine by physicians (3.5 ± 1.0). Residents were more likely to increase CLZ use with a point of care device for WBC (4.1 ± 0.9 vs. 3.5 ± 1.1, $p = 0.002$)and clozapine levels (3.9 ± 0.7 vs. 3.2 ± 1.03, $p = p < 0.0001$)compared to physicians in practice. Female physicians were more likely to increase clozapine use with a CLZ POC device compared to males. Sixty percent of physicians would like to use a handheld POC device (among 6 options); however, 14% would be interested in implantable devices. For the CLZ sensing we used an arrayed electrochemical microchip with 3 parallel chambers defined in polydimethysiloxane (PDMS). The microchip is based on 3×3 patterned gold working electrodes (radius of 100 μm for amplification characterization and 500 μm for functionality work).The chitosan film is biofabricated by application of 1.19 A/m^2 cathodic current density. Subsequently, the chitosan films are grafted with catechol by immersion in 5 mM catechol and application of 0.6 V vs. Ag/AgCl. The ability to amplify the CLZ signal with the redox cycling system demonstrated an anodic peak current density 2.46-fold higher than the unmodified electrode. We were able to detect reliably CLZ in 5, 25, and 50 mM buffered solutions.

Conclusions: Our work on the biosensor development demonstrates great feasibility for real-time analysis of CLZ. Likewise, the results of the physician survey demonstrate the need for this technology, particularly among younger prescribers. Psychiatrists feel their underuse of CLZ is hindered by frequent blood draws and welcome technology that could advance the ease of sensing blood levels and white blood cell levels and help close the loop in care. In addition, our biosensing data shows the sensitivity of combining the redox cycling system for CLZ signal amplification with the LOC paradigm of real-time and high throughput monitoring. In future work, we will focus on characterizing the detection limit and the dynamic range of the biosensor, with relation to the required clinical range and selectivity of the system for CLZ. Following performance characterization of the device with serum fluids, a flow system will be integrated to realize a fully autonomous micro-system for clinical monitoring of CLZ blood levels and white blood cells for schizophrenia patients. This will allow treatment teams to perform analysis at the point-of-care in a low cost, fast, and straightforward way aiming to guide CLZ dosages within the effective range, to decrease the patient's burden, and to personalize medical care.

Keywords: Clozapine Biosensor Blood levels Monitoring

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M189. Print 'Close the Use of a Novel Urine Drug Monitoring Test to Help Assess How Well Clinicians Predict Antipsychotic Medication Non-adherence

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Background: Prior research has established the critical role of maintenance antipsychotic pharmacotherapy in the management of schizophrenia, schizoaffective disorder, and bipolar disorder. Yet adherence to these drugs is a significant challenge for treating clinicians, and studies show that 50% of patients with these disorders do not take their antipsychotics consistently. Despite the key role of the prescribing psychiatrist in identifying and addressing non-adherence, relatively few studies have addressed how well psychiatrists and other prescribers are able to detect non-adherence. Furthermore, most of these studies relied on indirect measures such as pill counts, pharmacy refills, and electronic monitoring.

Methods: The current study utilizes a novel drug monitoring test to detect the presence of antipsychotic drugs and metabolites in urine and reports on the results of a pilot study comparing behavioral health clinicians' assessment of whether or not their patients were taking the antipsychotic(s) they prescribed as directed with the results of the urine monitoring test. Three psychiatrists and two psychiatric nurse practitioners working in a community mental health setting recorded their assessments for patients prescribed long-term antipsychotic medication. Subsequently, urine drug samples were obtained from these patients and analyzed for the presence of any of seven different antipsychotics using liquid chromatography/tandem mass spectrometry. The urine test result was then compared to the prescriber's assessment for the presence or absence of prescribed antipsychotic(s).
Results: Of the 47 patient samples, 37 were classified as coming from patients the clinicians predicted would have the antipsychotic medication present in their urine and 7 were classified as coming from patients where the clinician suspected non-adherence. Three samples had no clinician impression of status recorded. Of the 37 samples from patients believed to be taking their antipsychotic medication, drug was detected in only 28 samples. Thus, clinicians misclassified 9 out of 37 samples. Additionally, 15% (7/47) of samples also had a non-prescribed medication detected in the urine, while 17% (8/47) of the samples contained illicit drugs and/or alcohol.
Conclusions: Utilizing a novel laboratory technology that directly detects the presence of antipsychotic in urine, this study produced findings consistent with existing literature regarding the relatively poor accuracy of clinical assessment of antipsychotic non-adherence. Given the serious consequences of antipsychotic non-adherence, the use of an easily administered, highly sensitive laboratory test may afford clinicians a new tool to more accurately identify antipsychotic non-adherence.
Keywords: antipsychotic adherence, urine drug monitoring, liquid chromatography/tandem mass spectroscopy
Disclosures: M. Keats, Part 5: Ameritox, LTD; H. Leider, Nothing to Disclose; K. Bronstein , Part 5: Ameritox, LTD; M. Lang, Part 5: Ameritox LTD

M190. Functional Capacity Assessment in Older Adults

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Background: It is well recognized that people with severe mental illness (SMI) such as schizophrenia or those with cognitive impairments such as dementia or Mild Cognitive Impairment (MCI) often experience difficulty performing routine everyday tasks such as money or medication management that are critical to independent living. With the aging of the population, especially the increase in the 'oldest old' (aged 85 +), there are vast concerns about the increasing number of people who will experience cognitive problems that threaten their ability to live independently. Further, the number of adults with SMI in the community is increasing given advances in treatments for these illnesses and changes in treatment models. Thus, there is an increasing interest in developing tools to both detect the earliest manifestations of cognitive and functional decline in order to prescribe remediation strategies or to measures effectiveness of treatment approaches. Currently much of the assessment of functional performance is based on standardized neuropsychological measures of abilities, paper and pencil based tests of functional performance or informants' assessment of performance. The shortcomings of these measures have been widely documented. Ultimately, development of efficacious strategies to optimize functional performance requires understanding the performance of on actual tasks encountered in everyday life. This paper will discuss an innovative approach to functional assessment, which involves ecologically valid technology-based functional assessment battery that includes simulations of everyday activities that are important to independent living. Data will be presented from an on-going NIH funded trial that includes older adults with schizophrenia and non-impaired older adults regarding the feasibility and diagnostic sensitivity of the computer-based task battery. Information will also be presented on the relationships between component cognitive abilities and task performance.
Methods: The sample includes 80 male and female adults aged 50 + years with schizophrenia and 60 non-impaired adults aged 50 + years from a variety of educational and ethnic backgrounds who lived independently in the community and vary in cognitive status. All participants complete a battery of standardized neuropsychological measures of component cognitive abilities (MCCB) and standard measures of functional capacity (UPSA). They then perform the computer-based functional tasks that represent a variety of routine everyday activities including: using an ATM to perform banking transactions, a telephone menu system to refill prescriptions, a medication forms completion task, a shopping task and doctor's visit/medication management task. The >simulations are unique in that they present current technology-based versions of these tasks, which is important given the ubiquitous requirements for use of technology across all domains important to independent functioning. They are presented on a standard touch screen PC and available in English and Spanish.
Results: The task performance data included real time measures of accuracy, types of difficulties encountered by the participants and response times. Overall, the data indicate that use of this type of battery is feasible; all of our participants including those with limited computer experience are able to interact with and complete the task simulations. Importantly however, the tasks were also sensitive to detecting ability differences between the schizophrenia and non-impaired samples of older adults and within both samples. In general in addition to wide inter-group performance differences there were also wide intra-group performance differences. The data also indicated that component cognitive abilities were strong predictors of performance and variability in ability performance mappings.
Conclusions: Overall, our data indicate that a computer-based task assessment battery is a feasible and a useful tool for assessing functional performance in a variety of populations. Technology offers a flexible format that allows

for easy tailoring of the assessment protocols to meet the needs of unique populations or settings and the possibility of administering assessments and delivery interventions remotely outside of clinical settings such as the home, residential facilities or outpatient treatment centers.
Keywords: Functional capacity, disability, cognition, aging
Disclosures: S. Czaja, Nothing to Disclose; P. Harvey, Nothing to Disclose; D. Loewenstein, Nothing to Disclose.

M191. Estimating Endogenous Dopamine Levels at D2 and D3 Receptors in Humans Using the Agonist Radiotracer [11C]-(+)-PHNO

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Background: Using positron emission tomography (PET) and an acute dopamine depletion challenge it is possible to estimate endogenous dopamine levels occupying $D_{2/3}$ receptors (R) in humans *in vivo*. Our group has developed [^{11}C]-(+)-PHNO, the first agonist radiotracer with preferential in vivo affinity for D_3R. Thus, the use of [^{11}C]-(+)-PHNO offers the novel possibility of, i) estimating *in vivo* endogenous dopamine levels at $D_{2/3}$ R using an agonist radiotracer, and ii) estimating endogenous dopamine levels at D_3R in extrastriatal regions: substantia nigra, hypothalamus and ventral pallidum.
Methods: Tenhealthysubjects, four female, participated in the study (age = 29.1 ± 8.4). Participants underwent two [^{11}C]-(+)-PHNO PET scans: one under baseline conditions and the other after acute endogenous dopamine depletion. Dopamine was depleted via oral administration of alpha-methyl-para-tyrosine (AMPT) (64.28 mg/kg, in 6 divided doses) over a period of 25 h. For safety and monitoring purposes, all participants were admitted to a research bed at the Centre for Addiction and Mental Health for the entire duration of the dopamine depletion procedure. The percent change in [^{11}C]-(+)-PHNO binding potential non-displaceable (BP_{ND}) before and after dopamine depletion was used as an index of endogenous dopamine at $D_{2/3}$R at baseline. Our regions of interest included primarily D_2R regions (caudate and putamen), D_3R regions (substantia nigra, hypothalamus, and ventral pallidum), and mixed $D_{2/3}$R regions (ventral striatum and globus pallidus). We hypothesized that [^{11}C]-(+)-PHNO BP_{ND} would increase after dopamine depletion in every ROI except the substantia nigra, for which there is thought to be very little endogenous dopamine.
Results: AMPT-dopamine depletion significantly increased [^{11}C]-(+)-PHNO BP_{ND} in the caudate ($t(9) = 3.36$, $p = 0.008$), putamen ($t(9) = 5.84$, $p < 0.001$), ventral striatum ($t(9) = 10.87$, $p < 0.001$), and globus pallidus ($t(9) = 3.79$, $p < 0.001$). The average dopamine occupancy at $D_{2/3}$R was estimated to be 33.34% in the caudate, 33.44% in the putamen, 36.38% in the ventral striatum, and 11% in the globus pallidus. Due to poor model fitting, [^{11}C]-(+)-PHNO BP_{ND} could not be reliably estimated in the hypothalamus for one subject and in the ventral pallidum for four subjects. AMPT-dopamine depletion significantly increased [^{11}C]-(+)-PHNO BP_{ND} in the hypothalamus ($t(8) = 4.96$, $p = 0.001$). In the ventral pallidum, there was a trend for an increase ($t(5) = 2.32$, $p = 0.06$). The average dopamine occupancy at D_3R was estimated to be 68.5% in the hypothalamus and 64.8% in the ventral pallidum. Expectedly, [^{11}C]-(+)-PHNO BP_{ND} did not change in the substantia nigra after dopamine depletion ($t(9) = 0.29$, $p = 0.78$). The average plasma concentration of AMPT after 27 h of oral administration was 128(±53.7)umol/L. AMPT-dopamine depletion significantly decreased plasma levels of homovanillic acid (HVA) ($t(8) = 3.34$, $p = 0.01$) and 3-methoxy-4-hydroxyphenylglycol (HMPG) ($t(8) = 6.66$, $p < 0.001$) compared to baseline. HVA and HMPG plasma levels did not show correlation with change in [^{11}C]-(+)-PHNO BP_{ND}. Standard uptake values of [^{11}C]-(+)-PHNO into the cerebellum were not changed by AMPT-dopamine depletion.
Conclusions: The current investigation is the first to estimate endogenous dopamine levels at D_2R and D_3R in healthy humans using the agonist radiotracer [^{11}C]-(+)-PHNO. [^{11}C]-(+)-PHNO is sensitive to acute dopamine depletion in the dopamine D_2R-rich regions (caudate and putamen), the mixed $D_{2/3}$R-rich regions (ventral striatum and globus pallidus), and the extrastriatal D_3R rich regions (hypothalamus and ventral pallidum). Our current investigation demonstrates that PET imaging with [^{11}C]-(+)-PHNO can be employed for the estimation of endogenous dopamine at striatal and extrastriatal regions.
Keywords: PHNO, PET, dopamine, D3, D2, AMPT
Disclosures: A. Graff, Nothing to Disclose; F. Caravaggio, Nothing to Disclose; S. Nakajima, Nothing to Disclose; P. Gerretsen, Nothing to Disclose; D. Mamo, Nothing to Disclose; G. Remington, Nothing to Disclose; A. Wilson, Nothing to Disclose.

M192. Central 5-HT4 Receptor Binding as Biomarker of Serotonergic Tonus in Humans: A [11C]SB207145 PET Study

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Background: Identification of a biomarker that can inform on extracellular serotonin (5-HT) levels in the brains of living humans would enable greater understanding of the way brain circuits are modulated by serotonergic neurotransmission. Substantial evidence from animal studies and preliminary evidence from human positron emission tomography (PET) studies indicates an inverse relationship between central 5-HT tonus and 5-HT_4R density, suggesting that 5-HT_4R receptor density may be a biomarker marker for 5-HT tonus. Here, we investigated if a three-week administration of a selective serotonin reuptake inhibitor (SSRI), expected to increase brain 5-HT levels, is associated with a decline in brain 5-HT_4R binding.
Methods: Thirty-five healthy men were studied in a placebo-controlled randomized double-blind study. Participants were assigned to receive three weeks oral dosing with placebo or fluoxetine, 40 mg per day. Brain 5-HT_4R

binding was quantified at baseline and at follow-up with [^{11}C]SB207145 positron emission tomography.
Results: Three weeks intervention with fluoxetine was associated with a 5.2% reduction in brain 5-HT_4R binding ($p = 0.017$) whereas placebo intervention did not change 5-HT_4R binding ($p = 0.52$).
Conclusions: Our findings are consistent with a model, wherein the 5-HT_4R density adjusts to changes in the extracellular 5-HT tonus. Our data demonstrate for the first time in humans that the imaging of central 5-HT_4R binding may be used as an *in vivo* biomarker of the central 5-HT tonus.
Keywords: PET, 5-HT4 receptor, serotonin, fluoxetine
Disclosures: M. Haahr, Nothing to Disclose; P. Fisher, Nothing to Disclose; C. Gaden, Nothing to Disclose; V. Frokjaer, Nothing to Disclose; B. McMahon, Nothing to Disclose; K. Madsen, Nothing to Disclose; W. Baaré, Nothing to Disclose; S. Lehel, Nothing to Disclose; A. Norremolle, Nothing to Disclose; E. Rabiner, Nothing to Disclose; G. Knudsen, Nothing to Disclose.

M193. A Mixture Model Estimate of Time to Antidepressant Drug-Effect in Association with Covariates Using the STAR*D Sample

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Background: Until recently, studies seeking to make associations between human disease and genetic and environmental factors relied on disease phenotypes characterized by only one measurement. However, an increasing number of studies that use longitudinal phenotype data to investigate disease and drug effects have appeared, and analyzing results from these studies requires new methodology. Compared to analyzing single point measurements, determining how longitudinal measurements are associated with a disease's underlying factors (eg, clinical sub-phenotypes, age and genotypes) requires a more sophisticated model.
Methods: To meet this need, we developed a new statistical tool—the 'mixture model'—to analyze longitudinal data. This method can model onset of disease, or of drug effects. We further investigate the association between the onset of disease or drug effects and contributing factors such as genotype, age, and disease subtype. The new mixture model proposed here not only models a disease's development over time but also tests its associations with influential variables such as gender, age, and disease subtype. In order to estimate time of onset, data were divided into three stages: (1) incubation (for diseases) or drug naïve state (for drug effects); (2) onset; and (3) full-blown (disease) or palpable effects (drug). Our model requires sequenced phenotypic measurements covering all three stages, with time of onset, or turning point, marking the change between the asymptomatic/drug naïve stage and that in which disease symptoms or drug effects become manifest. In addition to estimating when onset occurs, our proposed statistical model takes into account any associations with potentially influential factors. Because evidence of disease or drug effect is assumed to be stationary during the incubation/drug naïve period, we used a classic stationary autoregressive model to determine time of onset (We used an Auto-Regression (1) model). Because the variability of symptoms after the onset of disease or drug effects requires models that can reflect change, a linear trend model was used. Because of missing data, it is difficult to directly estimate the maximum likelihood estimation (MLE) of the model parameters by maximizing the likelihood function. Thus we further propose an EM-based iterative algorithm to estimate the local MLE. Due to the space limitation, the mathematical details are omitted.
Results: The longitudinal phenotype data needed to implement this model typically have three parts: the incubation period, disease onset, and the disease manifesting period. The mixture model uses an expectation-maximization (EM)-based approach to estimate the distribution of disease onset. A solution for a weighed logistic regression on the outcome variables was used to estimate onset distribution. A log likelihood ratio test was used to evaluate the significance of the association between onset distribution and genotype or environmental factors. Extensive simulation studies, followed by application to longitudinal data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study were conducted to evaluate model performance and the model's overall utility. We selected longitudinal effect measures for time until response following treatment with citalopram, a selective serotonin reuptake inhibitor (SSRI) antidepressant. Our results indicated that the STAR*D participants with baseline anxiety reacted to the treatment two weeks later than the participants without baseline anxiety.
Conclusions: Our onset estimates were based on an EM-based iterative algorithm. Within the EM algorithm, we also proposed a novel method to estimate a weighted logistic regression model where the weights appear on outcome rather than probability, as often seen. The significance of any findings regarding the effects of particular variables on onset distribution is assessable by the traditional Likelihood-Ratio Test. To test the usefulness of this model, we used real world longitudinal phenotype data drawn from the STAR*D study, and investigated the onset of therapeutic effects associated with citalopram. Though any actual results drawn from this analysis must be considered preliminary, the mixture model was able to estimate the onset of drug effects and identify how various variables affected onset. Future studies will focus on different types of sequenced data under the mixture model framework.
Keywords: drug effect, drug onset, major depression, anxiety, association
Disclosures: Y. Yao, Nothing to Disclose; M. Xu, Nothing to Disclose; E. Murphy, Nothing to Disclose; H. Wang, Nothing to Disclose; F. McMahon, Nothing to Disclose.

M194. Responses to Blocked Goal Attainment in Preschoolers at Risk for Bipolar Disorder

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Background: Irritability is a stable dimension present in many psychiatric disorders, rendering it appropriate for the

Research Domain Criteria initiative (Insel *et al*, 2010). Although pediatric irritability does not appear to confer risk for adult bipolar disorder (BD) generally (Leibenluft, 2011), little is known about the longitudinal implications of irritability in children at familial risk for BD. Further, while BD has roots in early brain development, pathophysiological studies in early childhood are scarce. Thus, research in preschoolers at familial risk for BD could be informative. Studies of irritability in youth typically use paradigms that elicit frustration, defined as the emotional response to blocked goal attainment (Deveney *et al*, in press; Leibenluft, 2011). Few studies have examined frustration in preschoolers, and none focus on preschoolers at risk for BD. In preschoolers at high or low risk for BD, we compared behavioral and observational measures of irritability using two paradigms that involve blocked goal attainment. We anticipated that at-risk preschoolers would demonstrate lower frustration tolerance and deficits in anger modulation.

Methods: This study included 13 preschoolers at risk for BD (AR) [i.e., with a first-degree relative with BD ($M_{age} = 4.3$ years; 10 boys)], and 15 healthy controls (HC) matched on sex, age, and IQ ($M_{age} = 4.5$; 9 boys). We assessed responses to frustration using the Disruptive Behavior Diagnostic Observation Schedule (DB-DOS) and the 'Husker Farm' task. The DB-DOS is a standardized, structured observational paradigm for identifying clinically-significant disruptive behaviors in preschoolers (Wakschlag *et al*, 2008). It focuses on two domains—Anger Modulation (e.g., ease of elicitation, intensity, and pervasiveness of anger) and Behavioral Regulation (e.g., regulating behaviors in keeping with social rules and norms) across interactional contexts (parent versus examiner). Scores were coded from normative to atypical with scores of 2–3 considered clinically concerning. Preschoolers' behaviors were videotaped and coded. The 'Husker Farm' task, adapted from the Affective Posner task (Deveney *et al*, in press), is a computer-based behavioral paradigm developed to induce frustration in preschoolers. Children were asked to identify matches or mismatches of sounds and pictures of farm animals. The task consists of 4 non-frustration blocks (training, no reward, reward, debriefing) where correct feedback was provided and 1 frustration block (rigged feedback) where rigged feedback was given. Chi-square analyses were conducted to assess group differences in the proportion of children with observed problems in Anger Modulation and Behavioral Regulation on the DB-DOS. Two separate 2 (group: AR vs. HC) $\times$ 5 (block: training, no reward, reward, rigged, and debriefing) repeated-measures ANOVAs were used to examine accuracy and reaction time, respectively, on the Husker Farm. We conducted exploratory *t*-tests to compare performance between groups in specific blocks, considering the possibility of Type II error associated with small sample size.

Results: On the DB-DOS, nearly one-third of the AR group (31%, $n = 4$; $p = 0.03$), but no HCs, demonstrated two or more clinically-concerning problems in Anger Modulation during both examiner and parent interactions. Groups did not differ in Behavior Regulation ($p = 0.20$). Compared to HCs, more AR children had clinically-concerning levels of anger intensity (39%, $n = 5$; $p = 0.01$) and predominance (characteristically angry throughout tasks; 39%, $n = 5$; $p = 0.07$). In the Husker Farm task, a main effect of group indicated that ARs were less accurate than HCs across the task ($F = 6.06$, $df = 1, 18$, $p = 0.02$), with no group $\times$ block interaction ($p = 0.18$). However, exploratory *t*-tests indicated that the two groups differed in accuracy during reward/non-frustration (HC > AR; $t = 2.67$, $df = 19$, $p = 0.02$; $d = 1.16$) and rigged/frustration (HC > AR; $t = 2.64$, $df = 18$, $p = 0.02$; $d = 1.18$) blocks, but not during 'no reward' block.

Conclusions: Consistent with work suggesting that preschoolers at-risk for BD show behavioral disinhibition and difficulty modulating emotions (Hirshfeld-Becker *et al*, 2006), on the observational DB-DOS, preschoolers at risk for BD showed impairment in anger modulation marked by higher intensity and predominance of anger than low-risk preschoolers. Although there was no group $\times$ condition interaction on the Husker Farm behavioral task, exploratory *t*-tests in this small sample suggested that at-risk preschoolers may have impaired attention flexibility when rewards were involved and when experiencing frustration, evidenced by the large between-group effect sizes on these conditions ($d = 1.16$ and 1.18). Given the small sample size, these findings require replication. Future work examining the neural and clinical correlates of irritability in youth at risk for BD could be informative.

Keywords: Bipolar disorder, Risk factor, Irritability, Preschoolers, Frustration

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M195. Assessing Effort-based Decision-making in Schizophrenia with Two Novel Behavioral Paradigms

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Background: Negative symptoms significantly interfere with daily functioning among individuals with schizophrenia and are considered to be an unmet treatment need. Among the types of negative symptoms, it is the experiential negative symptoms (i.e., amotivation and anhedonia) that are the primary determinants of impaired functioning. Negative symptoms are a focus of treatment in psychopharmacological and psychosocial clinical trials. Currently, the evaluation of the negative symptoms of schizophrenia primarily relies on clinical interviews. Limitations of these assessments are that they depend heavily on the willingness of participants to disclose information and on the skills of the interviewer to elicit and score such information in a reliable fashion. Performance-based measures of motivation and effort could yield trial endpoints that may be more sensitive to treatment effects. Such measures are being developed for experimental studies with healthy subjects,

but have rarely been adapted and used in people with schizophrenia.

The goal of the current study is to assess motivation in schizophrenia using two newly-adapted effort-based decision-making tasks. We expect participants with schizophrenia to show a lack of willingness to exert effort for rewards, on both paradigms. Furthermore, we expect negative symptom severity to predict performance such that high negative symptom participants show less motivation and effort expenditure than participants with low levels of negative symptoms.

Methods: The data collection is ongoing and more data will be available at the time of the annual meeting. This abstract summarizes preliminary data on 20 participants with schizophrenia and 10 healthy controls. The schizophrenia participants were stabilized community outpatients and the mean age was 49 for both groups. Tasks: (1) Deck Choice Task. This task is based on an established paradigm used to measure willingness to exert cognitive effort for different levels of monetary rewards. In this computerized task, participants choose from one of two decks of cards, labeled as 'easy' or 'hard.' The 'hard' deck consists of cards that alternate between yellow and blue (each color requires a different mental activity). The 'easy' deck consists of cards that are all the same color (requiring no shifting of mental activity). The 'hard' option is paired with increasingly larger financial incentives (i.e., \$.10, \$.20, \$.40). The primary dependent variable is the ratio of low to high-demand choices. (2) Perceptual Effort Task. This task is based on the Five-choice Continuous Performance Test. In the adapted paradigm designed for this study, the task involves identifying a stimulus that varies in perceptual salience from the visual background. Task difficulty will be manipulated by adjusting the degree of contrast between the stimulus and background. The participant selects the preferred demand-level (easy, hard) while considering reward level (i.e., \$.10, \$.20, \$.40). The primary dependent variable is the ratio of low to high-demand choices. All participants complete the two effort paradigms, as well as measures of cognition and self-reported community functioning. Participants are also assessed on interview-based negative symptom measures. To obtain a range on negative symptoms, we are recruiting participants who are in the top and bottom thirds in terms of their scores on the SANS.

Results: For both tasks we used a 2 (group) by 3 (reward level) repeated measures analysis of variance. On the Deck Choice Task, significantly fewer participants chose the 'hard' option than controls, across all reward values ($F(2,54) = 22.5$, $p < 0.001$). Within the participant group, there was a significant difference in as participants with higher negative symptoms chose the easier option more frequently than those with lower negative symptoms ($F(2,36) = 19.4$, $p < 0.001$). For the Perceptual Effort Task, the participants selected the difficult option less often than controls ($F(2,56) = 10.2$, $p < 0.001$). In addition, the within-schizophrenia group comparisons were in the expected direction in that participants with high negative symptoms chose the easier option more frequently ($F(2,36) = 9.4$, $p = 0.001$).

Conclusions: As hypothesized, these preliminary results on two newly-developed tasks indicate that participants with schizophrenia are less willing to expend effort for rewards than controls as demonstrated by fewer choices of 'hard' on the two effort tasks. Further, we found a significant effect of negative symptoms such that participants who scored high on interview-based measures of negative symptoms are less likely to choose 'hard' tasks compared to those with low scores on negative symptoms. The two tasks placed different types of demands on subjects. One task required cognitive expenditure of effort and the other perceptual effort. Yet, both tasks showed the same pattern, both between participants with schizophrenia and controls, and within the schizophrenia group. These paradigms may be valuable for use in clinical trials as they provide objective indices of motivational (experiential) negative symptoms and do not rely on self-report. When the samples are larger, we will also examine the associations of these effort-based tasks with neurocognitive ability and daily functioning.

Keywords: Schizophrenia Negative symptoms Effort-based tasks Motivation

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M196. MCI and Everyday Task Performance

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Background: The concept of Mild Cognitive Impairment (MCI) has received considerable attention over the past few years, both as a clinical and research entity. Although controversy exists regarding the definition and assessment of MCI, it is generally thought of as cognitive impairment that is not a manifestation of normal aging. Currently little is known about the impact of MCI on routine/functional task performance. Many routine tasks such as medication or money management involve complex cognitive skills such as memory, attention, reasoning, and problem solving. Understanding the impact of MCI on the performance of everyday tasks is important to the development of strategies that enable people with MCI to live independently in the community. The goals of the study are to examine the impact of MCI on the performance of everyday tasks and to gather preliminary information on the relationship between cognitive abilities and task performance.

Methods: 30 participants (Normal:21, MCI:9) ages 55–84 (M 71.57, SD 7.99) were recruited. Eligibility criteria for MCI included memory complaint, global rating score on CDR of 0.5, no functional impairment or dementia as per DSM-IV TR criteria and MMSE greater or equal to 24. Participants were asked to perform cognitive assessments, demographic

and background measures and computerized functional task simulations, that included ATM, telephone voice menu and telephone answering machine simulations. These simulations were developed by our Center on Aging engineers.
Results: In the performance measure results for the answering machine task, there was statistical significance ($p = 0.05$) in the delayed score between participants with MCI (M 16.22, SD 3.77) and normal participants (M 17.64, SD 3.57). In the voice menu system task, significance ($p = 0.01$) was found between both groups in the total time result (M 30.76, SD 12.08 and M21.53 and 4.40 respectively). Correlation between different cognitive tests and functional tasks were statistically significant ($p = 0.01$) across the three tasks when looking at the entire sample and at MCI and healthy adults individually, most notably on the RVLT (immediate and retention), Trails B, digit symbol, CVLT delayed and COWA (raw).
Conclusions: Patients with MCI are able to perform relatively complex technology-based everyday tasks.The data suggest however, that MCI patients perform at lower levels than normal controls. >Cognitive abilities are related to task performance, and measures of these abilities may be useful predictors of performance difficulties. Patients with MCI are able to perform relatively complex technology-based everyday tasks. The data suggest however, that MCI patients perform at lower levels than normal controls. Cognitive abilities are related to task performance and measures of these abilities may be useful predictors of performance difficulties.
Keywords: Mild Cognitive Impairment (MCI) Functional Tasks Memory Everyday Task Performance
Disclosures: S. Sabbag, Nothing to Disclose; S. Czaja, Nothing to Disclose; P. Harvey, Nothing to Disclose.

M197. Differential Prefrontal Control of Brainstem Neuromodulatory Systems in Depression-related Behavior

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Background: The majority of currently available antidepressant drugs target at least one of the dopaminergic, serotonergic, or noradrenergic neurotransmitter systems. A central challenge in understanding the neural basis of depressive phenotypes has been to distinguish the separate functions subserved by these different brainstem neuromodulatory systems. Interestingly, the ventral tegmental area (VTA) and the dorsal raphe nucleus (DRN), containing dopaminergic and serotonergic neurons respectively, are both strongly controlled by glutamatergic afferents from the medial prefrontal cortex (mPFC), and these mPFC-neuromodulatory circuits have been implicated in the regulation of affective state. Here we report on the differential roles of the mPFC-VTA and mPFC-DRN projections in depression-related behavior in a rodent model.
Methods: ChR2(H134R)-EYFP was expressed in excitatory pyramidal neurons in the rat mPFC using an AAV5 viral vector with opsin under the control of the CaMKIIα promoter. Optical fibers were then implanted over either the VTA or the DRN, and mPFC axons in these regions were illuminated to activate these projections during the Forced Swim Test.
Results: We have previously shown that optogenetic stimulation of the projection from the mPFC to the DRN decreased immobility in the Forced Swim Test (FST) in rats. Here we tested activation of the mPFC-VTA projection, and whether the behavioral effects resulting from mPFC-DRN or mPFC-VTA stimulation could be quantitatively distinguished. Intriguingly, while stimulation of the mPFC afferents to both the VTA (Wilcoxon signed rank, $p < 0.001$, $n = 8$) and the DRN (Wilcoxon signed rank, $p < 0.001$, $n = 16$) produced an antidepressant-like reduction in immobility in the FST during illuminated epochs, stimulation of the mPFC-VTA projection led to a baseline increase in FST immobility relative to mPFC-DRN stimulation (Mann-Whitney U, $p < 0.001$). In addition, stimulation of the mPFC-VTA projection was attenuating, with a 69% reduction in the light-driven decrease in immobility over 4 repetitions (Mann-Whitney U, $p < 0.05$), while stimulation of the mPFC fibers in the DRN did not attenuate (Mann-Whitney U, $p = 0.22$).
Conclusions: Here we have reported on the differential roles of the mPFC-VTA and mPFC-DRN projections in depression-related behavior in a rodent model. These results may shed light on the comparative roles of these circuits in depression-related phenomena as well as in normal adaptive behaviors.
Keywords: depression, prefrontal, dorsal raphe nucleus, ventral tegmental area, optogenetics
Disclosures: M. Warden, Nothing to Disclose; E. Ferenczi, Nothing to Disclose; K. Deisseroth, Nothing to Disclose.

M198. Addiction-related Genes in Gambling Disorders: New Insights from Parallel Human and Pre-clinical Models

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Background: The worldwide expansion of legalized gambling has resulted in increased gambling-related harm, as observed by higher rates of bankruptcy, divorce and suicide secondary to excessive gambling involvement. It is estimated that ~ 2% of the population in the United States and Canada meet diagnostic criteria for disordered gambling. Neurobiological research supports the characterization of gambling disorder (GD) as a behavioral addiction. GD and substance addictions share dysfunctions in similar brain regions as well as performance on neuropsychological tasks. In particular, GD and substance dependent subjects present deficits in the Iowa Gambling Task (IGT), which assesses decision-making mediated by the prefrontal cortex. Regarding genetic vulnerability, it is estimated that 74% of the variance in the comorbidity between GD and alcohol dependence in men is accounted for by genetic factors. However, few studies have investigated the molecular underpinnings of GD. Recently, an animal model of gambling behavior based on the human IGT was developed (rat gambling task—rGT). We investigated whether rGT

performance and associated risk gene expression in the rat's brain could provide cross-translational understanding of the neuromolecular mechanisms of addiction in GD.
Methods: We genotyped tagSNPs in 40 addiction-related genes selected through the Knowledgebase for Addiction Related Genes (KARG). After quality control procedures and population stratification analysis, 211 tagSNPs were analyzed in a sample of 400 GD and 345 non-GD human subjects. A group of 12 rats had their baseline performance assessed on the rGT. Afterwards, the animals' brains were extracted and prepared for *in situ* hybridization and polymorphisms associated with GD in our human study were investigated to determine whether mRNA expression in rats was associated with the rat's performance on the rGT. All experimental protocols were approved by the Institutional Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals.*
Results: In humans, GD was associated with a *tag*SNP in *DRD3* (Nyholt corrected p-value = 2.6E-02), and showed a trend for association with *HTR2A* (Nyholt corrected p-value = 4.6E-02) and *CAMK2D* (Nyholt corrected p-value = 3.5E-02). In the animal arm, mRNA expression of these three genes in brains of rats was correlated with rGT performance specifically in areas known to be involved in reward processing and impulsivity: cingulate and piriform cortices (*Htr2a, Pearson's* $r = 0.65$, $p = 0.03$ and *Pearson's* $r = 0.61$, $p = 0.04$ respectively), Islands of Calleja (*Drd3, Pearson's* $r = 0.91$, $p = p = 8.96$ e-05) and amygdaloid nuclei (*Camk2d, Pearson's* $r = 0.66$, $p = 0.02$). After Bonferroni correction for 59 brain regions (total for 3 genes), only the association between rGT performance and *Drd3* expression remained significant (Bonferroni corrected $p = 0.005$).
Conclusions: An extensive body of pre-clinical research has implicated Drd3 in addictions, such as cocaine, methamphentamine, and tobacco dependence. Recently, a positron emission tomography study in humans reported a significant association of DRD3 binding with GD severity. Noteworthy, 85% of impulse control disorder cases (including GD) in Parkinson's disease patients are associated with the use of dopamine agonists, some of which are dopamine D2/D3 receptor agonists. Imaging studies have also found an association between impulse control disorders in Parkinson's disease and D2/D3 receptor availability in the striatum, providing further evidence for the involvement of D3 receptors in the development of gambling disorders. Together with our results, multiple lines of evidence validate the involvement of DRD3 in GD. Finally, our results also corroborate our previous report associating *HTR2A* with GD in a family-based association study. Similarly to the human arm, in the animal arm we found nominally significant associations between rGT performance and *Htr2a* and *Camk2d,* whereas the association with *Drd3* remained significant after correction for multiple comparisons. The rGT cannot address the full complexity of human GD; however decision-making deficits in the human Iowa Gambling Task have been consistently associated with GD. The brain areas most significantly correlated with rGT performance, such as the cingulate cortex, amygdala and the Islands of Calleja are likely candidates for the modulation of impulsivity and gambling-like behaviors. Using a similar animal model of gambling behavior, researchers have found a significant correlation between D2/D3 receptor availability in the striatum with higher wager (risk/reward) sensitivity, which supports our findings. To our knowledge, these three experiments (human genetics, behavioral model and gene expression) as a cross-translation paradigm have not previously been attempted in the field of addictions. The cross-validation of human findings in animal models is crucial for improving the translation of basic research into clinical treatments. If replicated, our results suggest that the use of human genetics, pre-clinical models and gene expression as a cross-translation paradigm could significantly accelerate neurobiological and pharmacological investigations in GD and possibly other addictive disorders.
Keywords: addiction, gambling disorder, animal models, candidate genes, gene expression
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M199. Effects of Combined Adrenoreceptor Antagonist Treatment with Prazosin and Propranolol on Alcohol Drinking in Humans and Rodents

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Background: Increased brain noradrenergic activity contributes to the pathophysiology of alcohol use disorder (AUD). The two major postsynaptic adrenoreceptors (ARs), the alpha-1 AR and the beta AR, both are potential pharmacotherapeutic targets for AUD. Here we report long term abstinence from alcohol use (17 years) in two Vietnam War combat Veterans with chronic PTSD. These Veterans had intractable AUD that resolved during treatment targeted at PTSD nighttime symptoms with the alpha-1 AR antagonist prazosin plus the beta AR antagonist propranolol. These clinical observations prompted studying the effects of combined prazosin and propranolol treatment on alcohol drinking in rats bred for high voluntary alcohol drinking and alcohol preference (P line).
Methods: (a) Human Observations: The first two Veterans ever prescribed prazosin as a potential therapeutic for chronic combat trauma posttraumatic stress disorder (in 1996) had comorbid treatment refractory AUD and suicidal ideation. Prazosin (titrated to 5 mg bid and 10 mg HS over 6 weeks) eliminated trauma nightmares and normalized sleep, but produced a reflex tachycardia which prompted addition of propranolol 20 mg tid to their regimens 6 weeks after starting prazosin. Alcohol use was quantified monthly for four months and then annually with the AUDIT-C. (b) Rat Studies: Two studies were performed in male P rats. In the first, the rats were injected with propranolol (10 to 20 mg/kg, IP) prior to daily 2-hour 15% alcohol access. In the second, rats were first allowed to become alcohol-dependent during prolonged (14 week) 24 h/day access to 20% alcohol. They were then injected (IP) with propranolol (0 to 15 mg/kg), or prazosin (0 to 2 mg/kg), or both propranolol and

prazosin, prior to daily 2-hour 20% alcohol access during the first week of withdrawal from 24 h/day alcohol access or following 3 weeks of subsequent imposed abstinence.
Results: (a) Human Studies: The two Veterans have remained totally abstinent from alcohol (AUDIT-C scores = 0) for 17 years. AUDIT-C score declined substantially during the 6 weeks of prazosin alone, but did not reach zero until two weeks after propranolol was added to prazosin. Suicidal ideation disappeared and has remained absent. The combined regimen was well tolerated. (b) Rat Studies: In the rat studies, alcohol drinking responses to propranolol alone were inconsistent. Combination treatment with prazosin plus propranolol was more effective than either drug alone for reducing alcohol consumption.
Conclusions: In persons with PTSD and comorbid AUD, the combination of prazosin plus propranolol may be effective for sustained remission of AUD. Our animal experiments support this hypothesis.
Keywords: PTSD, alcohol, prazosin, propranolol
Disclosures: M. Raskind, Nothing to Disclose; J. Froehlich, Nothing to Disclose; E. Peskind, Nothing to Disclose; D. Rasmussen, Nothing to Disclose.

M200. Postural Sway Abnormalities in Chronic Schizophrenia

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Background: Neurological soft signs (NSS), non-localizing abnormalities in sensory integration, motor coordination and inhibition, have become an important dimension in the study of schizophrenia. Assessment of NSS is typically assessed by observational methods of subject performance on specific tasks. Non subjective, quantitative measures have the potential to provide more reproducible and sensitive indices. Balance requires a broad range of neurological functioning and can be measured quantitatively using a force platform. Prior studies have found postural sway increases and increased postural instability in schizophrenia. In this study, we use an inexpensive force platform (Wii Balance Board - WBB) to evaluate postural sway in patients and controls.
Methods: Subjects consisted of 16 probands (9 male and 7 female, mean age 41) and 9 controls (5 male and 4 female controls, mean age 43). Only subjects 25 yrs and older were included in this arm of the study. There was no significant difference in age between groups. Probands were selected based on a consensus diagnosis. Balance measurements were performed for 60 sec for each of 3 tasks repeated 3 times per subject for a total of 9 measurements. The tasks performed included eyes closed, inspection, and search. All tasks required the subject to stand motionless on a WBB with feet shoulder-width apart. The inspection task requires the subject to fixate on blank sheet of paper, gaze within bounds at all times. The search task requires the subject to scan a paragraph of text counting the occurrences of a specified letter. During each task, custom software was used to collect center of pressure measurements at 50 Hz. Average sway distances were calculated in both the mediolateral (ML) and anteroposterior (AP) directions. Average distances are calculated as the total distance travelled in centimeters divided by the number of measurements collected (50 measurements per second) providing an average measurement of change over 1/20th of a second.Differences are then reported in cm/sec. Both between group and within group comparisons were performed based on task.The student's t distribution was used to evaluate whether observed differences were statistically significant.
Results: Significant between group differences were seen in AP sway during the search task. In patients with schizophrenia, postural sway was increased by an average of 0.173 cm/sec ($p = 0.039$) compared to controls. Neither the inspection task nor eyes closed task showed significant differences between groups. Within groups, significant differences were seen between the eyes closed task and each of the search and inspection tasks. Controls showed decreases in sway of 0.652 cm/sec ($p = 0.003$) for inspection and 0.817 cm/sec ($p < 0.001$) for search. Probands showed decreases in sway of 0.679 cm/sec ($p = 0.033$) for inspection and 0.979 cm/sec ($p = 0.001$) for search. There were no significant within group differences between inspection and search tasks.
Conclusions: Balance is complex and requires many physiological controls. If any are out of homeostasis, due to pathology or medication effects, disruption can be seen. This study shows that both controls and those with schizophrenia have the ability to decrease sway when challenged with a visual task. Further, those with schizophrenia are less able to decrease their sway as compared to controls. While the exact underlying cause is unknown, our findings show there are significant differences between those with and without schizophrenia both psychiatrically and neurologically. Future analyses will examine the relationship of balance measures with cognition, clinical and neuroimaging measures.
Keywords: schizophrenia, balance, measures sway, task
Disclosures: B. Nelson, ; K. Lim, Nothing to Disclose.

M201. Enhancement of rTMS Neuromodulatory Effects with Novel Waveforms Demonstrated via Controllable Pulse Parameter TMS (cTMS)

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Background: Repetitive transcranial magnetic stimulation (rTMS) is a widely used technique for studying brain function and is now approved for depression therapy. However, the neuromodulatory effects (e.g., changes in cortical excitability) of conventional rTMS are variable across studies, which might contribute to its variable effectiveness across clinical trials. For technical reasons having to do with the circuit topology, the majority of research studies and the approved therapeutic applications of rTMS use the conventional biphasic cosine pulse shape, although some reports indicate that this may not be very effective and other potentially more selective waveforms may have a better neuromodulatory performance (Taylor and Loo, 2007,doi: 10.1016 / j.jad. 2006. 06.027; Sommer

et al, 2013, doi:10.1016/j.brs.2012.07.003). We quantified changes in cortical excitability produced by different stimulation waveforms in comparison to standard biphasic cosine pulses, by using a controllable pulse parameter TMS (cTMS) device.
Methods: Twelve healthy subjects were recruited from the local community and screened for major axis I psychiatric disorders (MINI), drug abuse (urine test), and pregnancy (urine test). After an initial thresholding session, every subject went through four sessions of 1 Hz rTMS of the left motor cortex. In every session, the rTMS pulse had a different shape, randomly assigned from the following: conventional bidirectional cosine, bidirectional rectangular, or unidirectional rectangular in either posterior–anterior or anterior–posterior induced current direction. The current direction of the bidirectional pulses was the one having the lower motor threshold. For accurate coil placement, a robot arm (ANT Neuro, Netherlands) continuously corrected the coil position during each session. Excitability changes due to rTMS were measured by applying probing TMS pulses before and after the rTMS train and measuring the amplitude of the motor evoked potentials (MEPs) in the first dorsal interosseous.
Results: TMS was well tolerated and there were no adverse events. A mixed-effects model supported the hypothesis that the four different rTMS pulse shapes caused differing degrees of reduction in cortical excitability ($p<0.002$). Over the first nine minutes after the rTMS intervention for each condition, two rTMS pulse shapes generated significant reductions in excitability (reduction of MEP amplitude by 16% for the unidirectional P–A rectangular pulse, $p<0.02$; reduction by 9% for the bidirectional rectangular pulse, $p<0.04$). The unidirectional A–P rectangular pulse produced a pronounced trend with a reduction in MEP amplitude by 7%, $p<0.17$. The conventional biphasic cosine pulse produced a negligible increase of MEP amplitude by 3.8%, $p<0.21$.
Conclusions: The results demonstrate that pulse shape is an important factor in rTMS-induced changes in cortical excitability, and that the cosine pulse shape used in conventional rTMS devices is relatively less effective than rectangular pulses. The strongest reductions in excitability were observed for an asymmetric, unidirectional pulse, which is hypothesized to produce more selective neural stimulation than the conventional, more symmetric, bidirectional pulses. In agreement with the hypothesis of neuronal selectivity as the underlying mechanism, the same pulse with reversed current direction was less effective.
Keywords: Repetitive Transcranial Magnetic Stimulation (rTMS), waveform efficacy, neuromodulation, noninvasive brain stimulation, depression treatment.
Disclosures: S. Goetz, **Part 1:** SMG is inventor on several patents for medical devices, including TMS equipment, held by TU Munich and Duke University.; B. Luber, Nothing to Disclose; S. Lisanby, **Part 1:** Dr. Lisanby has been Principal Investigator on research grants to Duke from Brainsway, Neosync, and St Jude Medical and equipment support from Magstim and MagVenture., **Part 4:** Dr. Lisanby has been Principal Investigator on research grants to Duke from Brainsway, Neosync, and St Jude Medical and equipment support from Magstim and MagVenture.; C. Kozyrkov, Nothing to Disclose; W. Grill, Nothing to Disclose; A. Peterchev, **Part 1:** Dr Peterchev is Inventor on patents and patent applications on the cTMS technology used in this study, assigned to Columbia and licensed to Rogue Research; was Principal Investigator on a research grant to Duke from Rogue Research and equipment donations to Columbia and Duke by Magstim and MagVenture; and has received cTMS patent royalties from Rogue Research through Columbia University., **Part 3:** Dr Peterchev has received cTMS patent royalties from Rogue Research through Columbia University., **Part 4:** Dr Peterchev was Principal Investigator on a research grant to Duke from Rogue Research and equipment donations to Columbia and Duke by Magstim and MagVenture

M202. Computerized Cognitive Remediation for Geriatric Depression

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Background: Executive dysfunction in geriatric depression is common, leads to poor clinical outcomes and often persists despite remission of mood symptoms. This leaves patients perpetually vulnerable to disability and relapse. Specific executive functions, (i.e. susceptibility to cognitive interference and strategic semantic organization) appear to predict remission with conventional antidepressants. Neurobiologically-informed computerized cognitive remediation (CCR) can reduce both age-related cognitive decline, and some cognitive deficits associated with schizophrenia. This emerging CCR methodology, along with our findings in executive function provides an opportunity for a novel intervention. We developed a CCR intervention to target and treat executive dysfunction (ED) in geriatric depression (CCR-GD). Our assumption is that remediation of ED may modulate the underlying brain network abnormalities shared by ED and depression.
Methods: The objective of this study was to compare CCR-GD to a gold standard treatment (Lexapro: 20 mgs/12 weeks). We hypothesized that our targeted CCR treatment would improve both ED and depression in participants who had failed at least one trial of an adequate does of SNRI or SSRI. CCR-GD: Older adults (60–89) with major depression (by SCID-R/DSM-IV), who failed to achieve remission after treatment with therapeutic dosages of an SSRI or SNRI or at least 8 weeks. We also asked that they and their physicians had no plan to change medication or dosages for the duration of the study. 11 patients signed informed consent and entered the study (mean age = 73.5 years; sd = 7.8). 7 of 11 Patients were recruited after failing to remit during a controlled 12-week escitalopram trial from the ACISR. Of the 11 patients, 10 completed the four-week trial (91%). All 10 maintained the same medication and dosage throughout the trial. Participants underwent a neuropsychological battery at baseline and 4 weeks. Lexapro: Participants in CCR were matched to three elderly depressed historical control participants on three criteria: Age, depression severity, and executive dysfunction due to their demonstrable effect on clinical outcomes. All participants in both

studies met DSM-IV-TR criteria for unipolar major depression and had a score > 20 on the Montgomery-Asberg Depression Rating Scale (MADRS). Exclusion criteria: Major depression with psychotic features; other psychiatric disorders (except personality disorders); severe medical illness within the 3 months preceding the study; neurological disorders; medical conditions often associated with depression; drugs causing depression; MMSE score < 25; or current psychotherapy. Treatment: CCR: Participants completed 30 h of cognitive remediation on their own at the ACISR. There was no psychologist or psychiatrist intervention. Research assistants unaware of the study's hypotheses collected clinical ratings weekly. Lexapro: After a 2-week drug wash-out and single blind placebo lead-in, participants who still met DSM-IV-TR criteria for major depression received controlled treatment with fixed-dose escitalopram 20 mg daily for 12 weeks. Statistical Analysis: We first compared the groups on 6 clinically relevant variables using Mann-Whitney U statistics. Then, to assess for the significance of an interaction between treatment group and time in the trial we completed a longitudinal mixed models analysis with a random intercept and time in study, group, and a time by group interaction as fixed effects. The outcome variable was total MADRS score. As CCR is designed to remediate executive dysfunction, we attempted to compare the change in executive test scores (Trails B, Stroop CW) over time (baseline, end of study) by group using two repeated measures ANOVAs.

Results: There was no difference between the two groups in terms of baseline MADRS ($U = 180.0$, $p = 0.967$), age ($U = 173$; $p = 0.818$), education ($U = 141.5$; $p = 0.273$), age of onset $U = 153$; $p = 0.440$, or executive function (measured by Trails B) ($U = 152$; $p = 0.424$). There was not a significant overall group effect, $F(1,49.23) = 0.019$, $p = 0.892$, indicating that the two groups did not differ in their final MADRS score. There was a significant time effect, $F(1,71.22) = 30.97$, $p < 0.001$. In addition, the group by time interaction was significant, $F(1,61.8) = 5.32$, $p = 0.024$ suggesting that the two groups did differ in the length of time it took to respond to their respective treatments. The CCR participants MADRS scores dropped an average of 16.5 points over 4 weeks, 8 weeks faster than the Lex group. For the comparison of ED over time by group, the data indicated that CCR improved Trails B performance more than Lexapro ($t = 2.28$, $DF = 41$, $p = 0.027$); and that there was a trend for the Stroop Color-Word ($t = 1.86$, $DF = 41$, $p = 0.103$).

Conclusions: Deficits in executive function do not appear to change even after an effective course of medication, which leaves patients vulnerable to relapse. Though the data are preliminary, CCR-GD appears improve affective symptoms more quickly than Lexapro in patients who have previously failed to respond. In addition, CCR may improve both targeted and non-targeted executive functions while Lexapro does not.

Keywords: computerized cognitive remediation, geriatric, depression, executive dysfuction, escitalopram

Disclosures: S. Morimoto, Nothing to Disclose; B. Wexler , Nothing to Disclose; W. Hu, Nothing to Disclose; G. Alexopoulos, **Part 1:** Astra Zeneca, Avanir, Forest, Lilly, Merck, Navidea, Novartis, Otsuka, Pfizer, Sunovion, **Part 2:** Astra Zeneca, Forest, Merck, Sunovion, **Part 4:** Forest

M203. The Effect of Real Time fMRI Neurofeedback on Food and Cigarette Craving

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Background: Drugs of abuse and highly palatable foods activate similar neural circuits and abnormalities in these brain systems can often lead to addiction and, in the case of food, ingestive behaviors that resemble addiction. Cue-induced craving has been found to trigger disordered food intake and substance use behaviors as a result of dysregulation of two major brain systems: one involving hypersensitivity to rewarding cues and the other involving deficient cognitive control. Novel therapeutics targeting these disrupted brain systems could lead to enhanced treatment outcomes in these disorders. Real time fMRI (rtfMRI) neurofeedback is one novel tool may help people self-regulate their regional brain activity to improve control of these disrupted behaviors. The goals of this study were to test (1) whether neurofeedback training leads to improved self-control of inhibition-related brain activity in smokers and healthy-weight controls; (2) whether change brain activity is correlated with change in craving; and (3) whether rtfMRI neurofeedback training results in improved clinical outcomes compared two non-feedback control groups: cue exposure plus monitoring smoking behavior and monitoring smoking behavior only.

Methods: We collected data from 28 otherwise healthy, non-treatment-seeking cigarette smokers who were randomized to either two sessions of rtfMRI neurofeedback training ($n = 17$) or a non-neurofeedback control group (cue exposure plus monitoring ($n = 5$) or monitoring only ($n = 6$)). We also collected neurofeedback data from 16 healthy-weight (BMI < 25) control participants. The neurofeedback group performed a functional localizer task (Stop Signal Task) at each session in order to identify a region of interest (ROI) for neurofeedback training in the lateral inferior frontal cortex, an area involved in inhibitory control. Participants then attempted to self-regulate brain activity within this ROI while viewing smoking or food images. Follow up visits to assess smoking behavior were conducted one week and one month after the second neurofeedback training session in the smoking neurofeedback and control groups.

Results: Both smokers and controls reported a change in craving that correlated with the cognitive regulation strategy used ($p < 0.05$). In addition, compared to smokers, controls exhibited a trend towards increased inhibitory-control related brain activity following the first neurofeedback session ($p = 0.07$). However, change in brain activity did not correlate with reported craving in either group. Finally, both the neurofeedback and control group reported a significant reduction in craving to smoke and number of cigarettes smoked per day one week and one month following their neurofeedback training or clinic visit.

Conclusions: Overall, rtfMRI neurofeedback appears to be an intuitive, user-friendly tool that may lead to enhanced control of brain activity in healthy controls. However, we did not find evidence of learned control of brain activity or improved clinical outcomes in smokers after two neurofeedback sessions. It may be necessary to augment the current

approach by increasing the number of neurofeedback sessions, using adjunctive pharmacotherapy or cognitive training, or both. Finally, we recently convened a sponsored symposium to devise a research strategy to optimize rtfMRI neurofeedback for neurotherapeutic discovery and development (http://bit.ly/1c25GPW). Data collection from a modified neurofeedback paradigm based on the information exchanged at this symposium is ongoing.
Keywords: fMRI, neurofeedback, addiction, craving, food
Disclosures: L. Stoeckel, Nothing to Disclose.

M204. Orion Bionetworks: Causal Modeling Using Network Ensemble Simulations of Clinical, Imaging and Genetic Data to Predict Multiple Sclerosis

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Background: At its core, medicine seeks to establish causality. Orion Bionetworks is a unique, collaborative, non-profit partnership of leading organizations in patient care, computational modeling, translational research, and patient advocacy dedicated to transform our understanding of brain diseases, such as multiple sclerosis (MS), through the development of multi-scale computational bio-informatics models. In this pilot initiative, we have analyzed diverse high-dimensional genomic, transcriptome, and phenotypic data from a subset of patients in the Brigham Women's Hospital CLIMB multiple sclerosis longitudinal study using highly parallel supercomputing, machine learning and simulation and causal inference statistical methods. By causal inference we mean the process of uncovering causal relationships from data used, in this context, to uncover pathways involved in disease progression and brain atrophy.
Methods: Retrospectively collected longitudinal datasets including multiple MRI measures (including lesion volume and whole brain volume), EDSS scores, clinical, genomic (SNP) and transcriptomic measures from a database of 2500 subjects in the Brigham CLIMB study, meeting specific coherency criteria, were used to generate computational models developed using GNS Healthcare's REFS™ (Reverse Engineering and Forward Simulation) modeling platform, which utilizes Bayesian network inference and simulations. The mathematics behind causal network models are transparent and well documented[1,2,3,4]. GNS Healthcare's REFS™ platform uses highly optimized, proprietary machine-learning algorithms, run on massively parallel cloud-based supercomputers. Machine learning is used to extract the underlying structure from data and encode it in the form of causal network models. These networks represent causal relationships—not just correlations—in the data. Because the true structure underlying the data are uncertain, REFS™ uses a Markov Chain Monte Carlo algorithm to learn an ensemble of models. Simulations using these ensembles provides both a prediction and a confidence interval that measures the uncertainty about that prediction.
Results: Only 108 subjects met all criteria for coherency and were included in the initial model building. Subjects all had a diagnosis of relapse-remitting MS at study onset and were diagnosed early in their disease course and administered standard treatment. Subjects were longitudinally followed until they met criteria for relapse. All subjects had at least 2 MRI measures annually, clinical assessments every 6months and a single transcriptome assessment during their course of treatment. A network ensemble comprised of 1024 networks, were built from molecular, clinical and imaging measures from these subjects. We will present initial findings from simulations using these network ensembles including biomarkers of relapse, review the major pitfalls in using retrospective datasets for computational modeling, and present a design for prospective study collection that incorporates causal computational principles.
Discussion: Modern medicine has become ever-reductionist in its framing of medical diagnoses, neglecting the heterogeneity, interactivity and essentially systemic nature of disease pathogenesis. Most complex brain disorders are the emergent properties of multilevel hierarchical interactions within a human (genome to phenome) convoluted (influenced by) with external determinants (e.g. environment, microbiome, etc.). Since few disorders are the consequence of a single (gene) product abnormality, understanding their underlying pathogenic processes requires advanced methods to de-convolute the multiple layers that interact in this complex network, the human interactome. Through initiatives like Orion Bionetworks we seek to advance the computational methodology that will help us elucidate systems neurobiology by fostering interdisciplinary environments for patient - clinician - statistician - engineer engagement and iterative interaction.
Keywords: multiple sclerosis, computational, modeling, public-private partnership, causal inference, genetics
Disclosures: M. Haas, Nothing to Disclose; I. Khalil, **Part 1:** CoFounder and EVP of GNS Healthcare, **Part 2:** Employee of GNS Healthcare, **Part 3:** Employee of GNS Healthcare, **Part 5:** Employee of GNS Healthcare; P. De Jager , Nothing to Disclose.

M205. Specific Elevation of βCaMKII in the Lateral Habenula Lead to Core Symptoms of Depression

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Background: Hyperactivity in the l. habenula has emerged as a key brain region mediating depression, however the molecular mechanism underlying this activation remained unknown. Habenular inhibition induced via DBS appears to lead to symptom remission in the congenitally helpless rat and in the initial human trials. Thus understanding the molecular basis for the hyperactivity may lead to new treatment approaches and a better understanding of the pathophysiology of depression.
Methods: Using the congenitally helpless rat line as a depression model proteomics were carried out comparing protein levels in thebl. habenula of control non depressed rats and the cLH rats which had been tested and shown to be helpless and have increased swim time in the forced swim test. Using l. habenular tissue an unbiased quantitate proteomic scree was carried out using 15N stable isotope labeling comparing the cLH and non helpless control rats. Two further animal models were examined induced learned

helplessness and chronic mild stress. Using viral vectors we induced the changes seen in the rat models in mice and examined thier behavior. Paired whole cell patch recordings were carried out comparing viral infected cells with normal cells. RNAi technology was used to reverse the increases seen in the l. habeula of the cLH rats and thier beahvior analyzed.
Results: The proteomic screen revealed a specific 1.9 fold increase in βCaMKII with a less significant 1.3 fold increase in γCaMKII. Using induced LH or chronic mild stress also led to an increase in β CaMKII levels. Viral vectors were designed using the ubiquitane promotor for both α and β CamKII proteins and were shown to robustly increase tissue levels. When they were injected into the lateral habenula the β caused increased immobility times without changes in locomotor activity and anhedonia as measured by sucrose preference in contrast to the α form which caused no changes. Paired patch clamp recordings comparing virally infected cells and non-infected cells in tissue slices showed a highly large increase in mEPSC frequency (3.5x) and a 30% in = crease in amplitude. This was not seen in cells infected with α CaMKII. Using RNAi to knock down the enzyme in the l. habenula resulted in animals with reduced immobility time in the forced swim test and significantly increased escape frequency in the learned helplessness test.
Conclusions: These results suggest that the overactivity in the l. habenula which has been seen in tryptophan depletion studies in humans who become depressed is specifically caused by a tissue selective increased in βCaMKII, and this increase drives a range of depressive symptoms. Thus the reversal of these effects using RNAi suggests that it may be suffiecient to reverse the depressive phenotype by decreasing expression of this enzyme selectively in the l. habenula.
Keywords: βCaMKII, lateral habeunal, depression
Disclosures: H. Hu, Nothing to Disclose; H. Fritz, **Part 1:** Consultant Astra Zeneca 2011; K. Li, Nothing to Disclose; T. Zhou, Nothing to Disclose; Z. Yang, Nothing to Disclose; L. Liao, Nothing to Disclose; R. Malinow, Nothing to Disclose; J. Yates III, **Part 4:** Post Doctoral grant in lab from Roche involving autism, Consultant Thermo Fisher (mass spect)

M206. Mechanisms of Ventral Pallidal Enkephalin Regulation in Cocaine Addiction

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Background: Nucleus accumbens medium spiny neurons expressing enkephalin project mainly to the ventral pallidum (VP) as part of the indirect pathway. Inhibition of the indirect pathway was recently shown to block reinstatement of cocaine seeking, implying for enhanced activity of GABAergic input to the VP. Thus, proper modulation of the GABAergic input to the VP originating in the nucleus accumbens seems to be crucial for the maintenance of normal behavior. Opioids have been shown to act as modulators of synaptic release at many synapses. Specifically, striatal GABAergic input into the globus pallidus is modulated by opioids and disruption of this modulation has been shown in rat models of Parkinsonism. As cocaine self-administration seems to alter the activity of the indirect pathway we hypothesized that the modulation of GABA input to the VP by enkephalin is hampered.
Methods: Rats were trained to self-administer cocaine for two weeks followed by two weeks of extinction of cocaine-seeking. On the last day of extinction sagittal slices of the VP were prepared and GABAergic inhibitory postsynaptic currents (IPSCs) were recorded using thewhole-cell patch clamp technique.
Results: Opioid control of GABA neurotransmission in the VP is altered after withdrawal from cocaine self-administration. DAMGO, a μ opioid receptor agonist, inhibited GABA IPSCs in yoked-saline rats but not in cocaine-extinguished rats. In addition, CTOP, a μ opioid receptor antagonist, had little effect in yoked-saline rats, but significantly potentiated GABA IPSCs in cocaine-extinguished rats. Together, the evidence suggests the presence of tone on μ opioid receptors in the VP after extinction of cocaine self-administration. We then examined the consequences of such tone on μ opioid receptors in the VP. Interestingly, we found that high frequency stimulation of nucleus accumbens input to the VP in yoked-saline rats resulted in μ opioid receptor-dependent long term depression of GABA IPSCs (LTD_{GABA}). This LTD_{GABA} was lost in cocaine-extinguished rats or in slices of yoked-saline rats in the presence of DAMGO or CTOP.
Conclusions: Self-administration of cocaine followed by extinction learning causes enduring changes in the opioid system in the VP. These changes result in the loss of opioid modulation of GABA neurotransmission and consequently in altered plasticity in GABAergic synapses. This may underlie, at least in part, the addictive properties of cocaine mediated by the indirect pathway.
Keywords: Ventral Pallidum, Cocaine, Enkephalin, GABA, Long Term Depression
Disclosures: Y. Kupchik, Nothing to Disclose; P. Kalivas, Nothing to Disclose.

M207. Abnormalities in Striato-pallidal-thalamic Surface Morphology as an Endophenotype for Obsessive-Compulsive Disorder

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Background: While OCD is highly heritable ($h2 > 0.5$), the exact genes conferring risk are largely unknown (1). Approaches that might accelerate genomic progress are thus a priority. Neural changes found in unaffected relatives that are similar but often less severe than those present in affected siblings have been proposed as endophenotypes. These changes reflect genetic lability to OCD and may lie close to the neurobiology of the disorder and has proved powerful in delineating anomalous brain activity associated with genetic risk for the disorder (2). Here we extend the focus to neuroanatomic change in the striatum, globis pallidus and thalamus, interconnected structures that have been repeatedly implicated in OCD. We use a novel method to define surface morphological change at a submillimeter level of spatial resolution. We thus aimed to map differences in subcortical surface morphology in OCD. Additionally we determined whether these changes are present in the

unaffected siblings of those with the disorder, constituting endophenotypes for future studies.
Methods: 22 patients with OCD (14 male; mean age 24, SD 13, range 10 to 50 years) and 25 of their unaffected siblings (14 male; mean age 25, SD 9; range 10 to 45years) were contrasted against 47 age and sex matched healthy controls. OCD was diagnosed by the Structured Clinical Interview for DSM-IV Disorders and symptom severity was estimated by the Yale-Brown Obsessive-Compulsive Scale (YBOCS). The study was approved by the IRB of the NIMH and all individuals gave written informed consent. T1-weighted neuroanatomic resonance images were acquired on 1.5-T General Electric Signa scanner, using 3D spoiled gradient recalled echo in the steady state. Definition of the subcortical surface morphology used a novel a multi-atlas based approach which matched each individual's subcortical structures to multiple manually labeled templates (3). This estimates surface area at $\sim$6000 vertices for the striatum; $\sim$4000 for the thalamus and $\sim$1000 for the globus palldius. A mixed model ANOVA tested for overall group differences in vertex level surface areas. A random term for family identity was included to account for familial relatedness. Within the regions of overall group difference we defined endophenotypic regions as those where both the OCD and unaffected siblings differed significantly and similarly from controls (ie [OCD > controls] AND [Unaffected sibs > controls]). To control for multiple comparisons, permutation testing was used get the correct distribution of the appropriate test statistic under a null hypothesis for both the group ANOVA and planned post-hoc pairwise comparisons. Alpha was set at $p < 0.05$.
Results: Symptom severity was higher in the OCD probands (Y-BOCS mean 24, SD 13) than the unaffected siblings (mean 2, SD 3, $t = 10.2$, $p < 0.0001$). Eleven probands were taking SSRIs or clomipramine at time of the study. In the mixed model ANOVA, significant overall group differences were found bilaterally in the head and tail of caudate; the globus pallidus , pars interna; and the thalamus, in the region of the anterior and dorsomedial thalamic nuclei. The planned pairwise contrasts then defined regions where both the OCD and unaffected siblings differed from controls. These localized to the head and mid-tail of the caudate, and the right thalamus, in the area of the dorsomedial and anterior nuclei. For these caudate regions, the surface area of the controls (mean 183 mm2, SD 14,6) was significantly less than both the unaffected siblings (mean area 195, SD 21, $t = 2.4$, $p = 0.03$) and OCD probands (mean area 184, SD 14, $t = 4.01$, $p = 0.0006$). In the region of the dorsomedial and anterior thalamus, the controls had reduced surface area (mean 61 mm2, SD (6) compared to both the unaffected siblings (mean 66, SD 10, $t = 2.5$, $p = 0.02$) and the affected probands (mean 69, SD 10; $t = 3.5$, $p = 0.002$). In these regions, there was a significant linear trend ($p < 0.05$, 1000 permutations). That is, the unaffected siblings occupied an intermediate position between their affected sibs and controls. Results held when analyses were confined to the 11 probands who were unmedicated at the time of the study.
Conclusions: We define a pattern of subcortical morphological change shared by those with OCD and those carrying a genetic liability for the disorder. The increase in surface area localized to richly interconnected regions of the caudate and thalamus that support complex executive functions which are impaired in OCD, such as planning, implicit learning and cognitive control. Generally, in these regions there was a significant linear increase in surface area, moving from controls through unaffected sibs to those with OCD. Surface morphological changes in striato-pallidal-thalamic circuitry emerge as endophenotypes for future genomic studies.
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Keywords: Obsesssive-Compulsive Disorder; Striatum; Thalamus; Systems Neuroscience; Endophenotype
Disclosures: S. Phillip, Nothing to Disclose; W. Sharp, Nothing to Disclose; J. Rapoport, Nothing to Disclose.

M208. High Blood Cytokine Levels are Linked to Decreased Verbal Fluency and Broca's Area Volume Reduction in Schizophrenia

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Background: There is increasing evidence for the role of the immune system in the pathogenesis of schizophrenia. We predicted a subset of people with schizophrenia would display increased immune activity which would be related to more severe cognitive and structural brain abnormalities.
Methods: In 42 patients with schizophrenia and 42 age and sex matched controls we assayed cytokine mRNA (IL1β, IL8, IL6, IL18 and IL2) from white blood cells, cognition and structural MRI.
Results: Applying a two-step clustering algorithm, we identified two subgroups characterized by either high ($n = 35$) or low ($n = 49$) cytokine levels. The high inflammatory group contained significantly more people with schizophrenia ($n = 22/35$) than controls ($n = 13/35$, $\div 2 = 3.97$, $p < 0.05$). There was no IQ difference between high and low inflammatory groups; however, verbal fluency was significantly lower in the high inflammation group, $t(40) = -2.32$, $p < 0.05$. A forward stepwise linear regression showed that IL1β mRNA had a significant inverse relationship with verbal fluency in schizophrenia, $\beta = -0.35$, $F(1,40) = 5.51$, $p = 0.02$. The schizophrenia high/low inflammatory groups ($n = 36$) differed significantly across language region volumes in the left hemisphere, $F(4,26) = 3.38$, $p = 0.02$. Post-hoc analysis showed only the left pars opercularis volume was significantly (15%) smaller in the high inflammatory group, $F(1,29) = 5.31$, $p < 0.03$.
Conclusions: These results show that increased levels of peripheral immune mRNAs are significantly related to both poorer verbal fluency and reduced Broca's area brain volume in schizophrenia. These results raise the possibility of administering anti-inflammatory treatments that may re-

verse language deficits and associated brain abnormalities in subgroups of people with schizophrenia identified by immune related biomarkers.

Keywords: schizophrenia, cytokines, IL-1beta, language, Broca's area

Disclosures: T. Weickert, Nothing to Disclose; S. Fillman, Nothing to Disclose; R. Lenroot, Nothing to Disclose; J. Bruggemann, Nothing to Disclose; M. O'Donnell, Nothing to Disclose; S. Catts, Nothing to Disclose; C. Weickert, Nothing to Disclose.

M209. 5-HT3 Receptors Are Involved in the Mechanism of Action of the New Antidepressant Drug Vortioxetine

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Background: Vortioxetine (Lu AA21004) is an investigational antidepressant [1] under clinical development for the treatment of major depressive disorder. In cell studies, vortioxetine is a 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist, and inhibitor of the serotonin (5-HT) transporter (SERT) [2]. Analyses of target occupancies in the rodent brain and SERT occupancy studies from human PET studies support a dose dependent occupancy of all these targets at clinical doses of vortioxetine [2, 3]. Vortioxetine increases the extracellular monoamine concentration in the forebrain to a greater extent than the selective serotonin reuptake inhibitors (SSRIs) [2,3]. This difference is likely due to the additional pharmacological activities of vortioxetine at 5-HT receptors, which may prevent local and distal self-inhibitory feedback mechanisms controlling monoaminergic activity. The aim of the present study was to explore the role played by 5-HT_3 receptors (5-HT_3-R), for which vortioxetine shows high affinity (Ki = 3.7 nM). 5-HT_3 receptors are present in the forebrain on GABAergic interneurons that control pyramidal neuron activity in the hippocampus and the prefrontal cortex (PFC) [4]. 5-HT_3-R blockade may, therefore, alter the functional connectivity between the PFC and the midbrain, increasing the PFC excitatory tone onto serotonergic neurons.

Methods: We examined the effects of vortioxetine, the selective SERT inhibitor escitalopram and the 5-HT_3-R antagonist ondansetron on the firing activity of medial PFC (mPFC) pyramidal neurons projecting to midbrain in anesthetized male Wistar rats, using extracellular recordings. Pyramidal neurons were identified by antidromic stimulation from the dorsal raphe nucleus and, in some instances, also from the ventral tegmental area. After obtaining a stable baseline recording for 5 min, drugs were administered i.v. and recordings were made for an additional 22–40 min. Electrode localization was performed by histological verification in frozen brain sections.

Results: Vortioxetine (0.1–1.6 mg/kg i.v., cumulative doses) dose-dependently increased the discharge rate of pyramidal neurons in the medial PFC (mPFC), with a maximal effect at 0.4 mg/kg i.v. (297% of baseline) which persisted for >15 min after last injection. The administration of escitalopram (0.1–1.6 mg/kg i.v., cumulative doses) did not significantly alter the discharge of mPFC pyramidal neurons. However, the selective 5-HT_3-R antagonist ondansetron (0.16–1.28 mg/kg i.v., cumulative doses) evoked a dose-dependent increase of pyramidal discharge in ca. 70% of the neurons recorded. The maximum effect was achieved at 1.28 mg/kg i.v. and the increased discharge persisted for >20 min after administration of the last dose. Likewise, the combined i.v. administration of escitalopram (0.1 mg/kg) and ondansetron (1.28 mg/kg) evoked a 3-fold increase of the discharge rate of mPFC pyramidal neurons projecting to midbrain.

Conclusions: Vortioxetine dose-dependently increases the discharge rate of mPFC pyramidal neurons projecting to midbrain, with a maximal effect at 0.4 mg/kg i.v. whereas escitalopram does not significantly alter the discharge rate of mPFC pyramidal neurons at doses that fully block SERT. The 5-HT_3-R antagonist ondansetron evokes a dose-dependent increase of pyramidal discharge at doses that block physiological 5-HT activation of GABAergic interneurons [4]. This indicates that the activity of mPFC pyramidal neurons projecting to midbrain is tonically inhibited by 5-HT_3-R, despite the different layer distribution of GABA interneurons expressing 5-HT_3-R (layers I-III) and of pyramidal cells projecting to midbrain (mainly layer V). The effect of vortioxetine on pyramidal cell discharge is mimicked by the combination of escitalopram + ondansetron. The effect of the combination appears to be additive. Overall, the present data suggest that vortioxetine modulates the activity of PFC neurons through the blockade of an endogenous tone on 5-HT_3-R. This receptor appears to be localized mostly in layer II/II GABA interneurons controlling synaptic inputs onto apical dendrites of layer V pyramidal neurons.

Keywords: 5-HT3 receptor, Antidepressant, Vortioxetine, GABAergic interneurons, Pyramidal Neurons, Prefrontal Cortex, Dorsal Raphe Nucleus

Disclosures: F. Artigas, **Part 1:** Prof. F Artigas declares having received consultancy fees from H. Lundbeck A/S., **Part 4:** Work order Number 01: Mechanism of action of LuAA21004: focus on 5-HT receptors , Master Collaboration Agreement between CIBERSAM and H. Lundbeck A/S,(2012 – 2013) IP: Francesc Artigas ; M. Riga, Nothing to Disclose; P. Celada, Nothing to Disclose; C. Sanchez, Nothing to Disclose.

M210. Implications of the Human Mu Opioid Receptor (OPRM1 A118G) Polymorphism in the Neurobiology of Stress and Placebo Responses

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Background: OPRM1 are critically involved in the modulation analgesia, reward and responses to stress. To further understand the human implications of the OPRM1 in these processes, we investigated the role of a commonly occurring non-synonymous SNP (rs1799971; OPRM1 A118G), which results in an amino-acid substitution (Asn40Asp or N40D) in the N-terminal region of the mu-opioid receptor, on psychophysical and neurotransmitter (dopaminergic, opioid) responses to pain and placebo-induced analgesia in humans.

Methods: Fifty six subjects were genotype for the *OPRM1* A118G polymorphism and underwent a sustained pain challenge with and without placebo administration and positron emission tomography (PET) measures of μ-opioid and dopamine (DA) $D_{2/3}$ receptor mediated neurotransmission with [^{11}C] carfentanile and [^{11}C] raclopride. Personality scores using the NEO-PI-R and several pain and affect measures were collected.
Results: *OPRM1* AA homozygotes, compare to G carriers,-showed an overall increase in μ-opioid receptor availability at baseline, which was negatively correlated with the NEO-Vulnerability and Depression scores in regions implicated in pain and affect regulation, such as the subgenual anterior cingulate, the thalamus and the hippocampus. *OPRM1* AA homozygotes also showed increased placebo induced μ-opioid and $D_{2/3}$ activation in several regions, including the anterior insula, the amygdala, the nucleus accumbens (NAc), the THA and the brainstem; in addition, AA homozygotes showed a blunted DA response in the NAc in response to stress. Placebo-induced activation of μ-opioid neurotransmission in the NAc was positively correlated with reductions in the affective dimension of pain and the Total Mood Disturbance scores of the volunteers. At a behavioral level, AA homozygotes, compared to G carriers, showed decreases in negative affect after placebo administration and lower NEO-Neuroticism scores (Vulnerability and Depression).
Conclusions: Our results provide a mechanistic approach to the effect of the *OPRM1* A118G on responses to stress and placebo analgesia. Individuals carrying the G appear to have a vulnerability phenotype, defined by a lower OPRM1 density, decrease placebo induced μ-opioid and DA $D_{2/3}$ activation after placebo, increase DA response to a pain challenge and higher NEO-Vulnerabiltiy and NEO–Depression scores. These results provide initial evidence for the development of biomarkers in illness where vulnerability to stress represents a core feature, such as depression.
Keywords: OPRM1, opioid, dopamine, placebo, stress
Disclosures: M. Pecina, Nothing to Disclose; T. Love, Nothing to Disclose; C. Hodgkinson, Nothing to Disclose; D. Goldman, Nothing to Disclose; C. Stohler, Nothing to Disclose; J. Zubieta, Nothing to Disclose.

M211. Pattern Classification Accuracy to Taste Stimulation in Eating Disorders

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Background: The eating disorders anorexia (AN) and bulimia (BN) nervosa are severe psychiatric disorders with high mortality. Brain imaging has helped to better characterize brain pathology in eating disorders. For instance neurotransmitter receptor studies have shown that AN and BN are associated with distinct serotonin and dopamine receptor alterations that were frequently related to measures of anxiety. Functional magnetic resonance imaging (fMRI) indicated that anxiety circuits in eating disorders are hyper responsive, and studies using taste stimuli indicated that AN and BN are associated with opposite response in the insula and striatum. Those studies measured strength of signal within clusters across groups. It is unclear however, whether specific patterns of activation across voxels within regions of interest can be identified, which would be a step toward characterizing neuronal patterns. It is now possible to 'decode' the activation clusters, and identify patterns of voxel activation within the cluster and use those as a measure of how accurately those patterns can classify the stimulus. Such procedures can thus create a 'fingerprint' of brain response to visual, taste or other stimuli. In this study we tested whether we would find altered patterns of voxel activation in the insula, the primary taste cortex, between women currently ill with AN or recovered from AN (REC AN), women with BN or obesity (OB), compared to healthy control women (CW) in response to taste stimuli. We hypothesized that food restriction would be associated with higher pattern classification accuracy, while excessive food intake would be associated with lower accuracy compared to healthy controls.
Methods: We recruited 111 subjects, 27 healthy CW, 21 women with restricting type AN, 24 REC AN women (restricting type), 20 women with BN, and 19 women with OB. All subjects underwent functional magnetic resonance imaging, during which they received sweet taste (sucrose), which was contrasted against no stimulus or artificial saliva. Brain imaging data were analyzed using multivariate Bayesian decoding of the brain images. That approach identified from the overall activation within the insula (defined by a standard template) patterns of activation across voxel groups, partitions or subsets of voxels that differ in variance of activation. A greedy search algorithm was used to define in a hierarchical pattern the number of partitions that can be associated with the stimulus. Log evidence identified the partition model with the highest significance for each subject as well as across groups as an indicator of pattern accuracy matched to the stimulus. ANCOVA was used to contrast groups for partition log evidence and comparisons were controlled for medication use as well as comorbidity.
Results: Sweet taste pleasantness was similar across groups ($F = 1.369$, $p < 0.245$). All subjects showed a sparse distribution of pattern activation. Contrast sweet taste versus no stimulus: Chi-square test indicated similar proportion of partition classifications across all groups ($p < 0.440$). The majority of subjects in each group showed the highest log evidence for partition seven and those subjects were further compared across groups (CW $n = 19$, REC AN $n = 19$, AN $n = 11$, BN $n = 13$, OB $n = 12$). The number of voxels activated was similar between groups ($p < 0.102$). Log evidence was significantly different across groups ($F = 3.633$, $p < 0.010$). Post hoc tests indicated AN > CW ($p < 0.007$), AN > REC AN ($p < 0.030$), AN > BN ($p < 0.031$), and AN > OB ($p < 0.001$). For the contrast sweet taste versus artificial saliva, partition seven was also the predominant model solution, but there was no significant difference across groups.
Conclusions: This study indicates that within the insula there can a different pattern of voxel activation be identified in response to taste stimuli in AN compared to CW, BN, OB as well as REC AN. This does not seem to be specific to sweet taste but rather to any taste. Furthermore, this appears to be a state dependent marker that remits with

recovery. This study therefore further highlights the insula as a key structure in the pathophysiology of AN and it should be a target for intervention. Food restriction appears to be associated with increased pattern strength that can be modulated by weight gain and recovery, with an inverese relationship between weight status and pattern strength. While the underlying neurotransmitter function is unknown and larger studies for replication are needed, this study suggests that weight state is associated with altered neuronal pattern activation.

Keywords: Eating Disorder Anorexia Nervosa Decoding Insula Pattern Classification

Disclosures: G. Frank, Nothing to Disclose; C. Keffler, Nothing to Disclose; M. Shott, Nothing to Disclose.

M212. Whole-brain Dynamics are Shifted in Animals with Learned Helplessness

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Background: Defining the neuronal circuits underlying depressive-like behavior in animal models can identify new targetable pathways for treatment of depression. We have explored whole-brain activity patterns in depressive-like behavior and resilience using the rat learned helplessness paradigm by quantifying immediate early gene c-Fos expression, and metabolism with 2-deoxy-2[^{18}F]fluoro-D-glucose positron emission tomography (^{18}FDG-PET). Our goal was to compare whole-brain activity patterns and region-by-region relationships that defined helplessness and resilience in order to extrapolate circuits mediating these behavioral phenotypes.

Methods: We have evaluated neuronal activity in male Sprague-Dawley rats (3–5 months old) characterized as either learned helpless or resilient using two approaches; a novel methodological application of whole-brain c-Fos quantification ($n = 14$; 9 helpless and 6 resilient) (Kopec *et al*, 2011) and in vivo ^{18}FDG-PET metabolic neuroimaging ($n = 16$; 8 helpless and 8 resilient). These two approaches are commonly used outcome measures for neuronal activity and are thus highly complementary. c-fos provides cellular level resolution (albeit at a terminal end point), and small animal^{18}FDG-PET provides *in vivo* evidence of brain activity (though with limited spatial resolution, ~ 2 mm). Therefore, c-fos and metabolic PET when used in conjunction provide a consonant representation of regional brain activity levels associated with behavior. Specifically, we quantified c-fos expression in approximately 300 individual brain regions for each rat, and metabolic activity in over 50 regions using in house-developed whole-brain templates.

Results: We discovered that helplessness embodies a specific brain-wide activity pattern characterized in part by enhanced inter-cortical relationships. Furthermore, we found that brain-wide activity in individual resilient animals did not coalesce into a specific pattern, suggesting several unique circuit mechanisms can generate a resilience phenotype. For our analysis, we calculated whole-brain correlation coefficients for each pair of animals in order to determine how congruently c-Fos expression, or metabolic activity, levels fluctuated among all individual brain regions. Strikingly, the pattern of correlations describing the resilient phenotype significantly diverged from helplessness for both c-fos ($p = 3.33 \times 10^{-5}$) and ^{18}FDG-PET ($p = 4.30\text{x}10^{-6}$) cohorts suggesting similar neuronal activity profiles in all helpless animals, but more variability in overall brain activity among resilient animals. A hierarchical clustering analysis also confirmed that brain-wide neuronal activity in helpless animals tended to reflect a common pattern unlike resilient animals. We are currently exploring individual brain regions that embody this common helplessness pattern and identifying those brain regions that diverge between helplessness and resilience, particularly in the detailed map provided by whole brain c-fos analysis. In the cortex for example, significantly positive correlated regions in helplessness, but not resilience, included cingulate, infralimbic, prelimibic, dorsal peduncular and endopiriform cortices. In contrast, significantly correlated regions in resilience but not helplessness included retrosplenial, auditory, perirhinal, parietal, sensory, and motor cortices.

Conclusions: Our study demonstrates utility in comparing brain-wide activity patterns for reveling circuits driving specific behaviors. Overall, these data suggest whole brain dynamics are funneled into a specific pattern leading to the helplessness phenotype, whereas differing and more flexible patterns of brain activity embody resilience. The specific enhanced correlative activity in prefrontal regions of helpless animals is reminiscent of that observed in depressed human patients with neuroimaging. With regards to helplessness, our data suggest a dynamic shift in cortico-cortical neuronal connections, particularly involving enhanced positive correlations in the dorsal and ventral medial prefrontal areas, and deficient synchronous activity in cortices involved in multisensory integration, memory, and coordinated movement. Ongoing analysis of this rich data set will reveal further detailed changes in circuit activity underlying helplessness behavior.

Keywords: c-fos, helplessness, resilience

Disclosures: M. Mirrione, Nothing to Disclose; B. Li, Nothing to Disclose; S. Shea, Nothing to Disclose; H. Fritz, **Part 1:** Consultasnt Astra Zeneca 2011–12

M213. Sleep Misperception in Bipolar Disorder: Are Our Patients Getting 7 H of Sleep?

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Background: Sleep disturbance is common in bipolar disorder (BD) and can be a trigger for mood episodes. Treatment decisions are made in the clinic based on self-reported sleep duration, bedtime and waketime. However, BD may influence a patient's perception of sleep. In primary insomnia, objective short sleep duration (i.e., < 6 h) is associated with cardiometabolic morbidity and mortality, while sleep misperception is associated with increased depression and anxiety. We aim to describe patterns of sleep misperception in BD.

Methods: BD ($n = 27$ and HC ($n = 23$) subjects wore an actigraph for one week on the non-dominant wrist and simultaneously filled out a sleep log. Subjects were given a diagnostic interview, the Hamilton Depression Rating Scale, the Young Mania Rating Scale, and the Epworth Sleepiness Scale. Actigraphic sleep variables were computed with ActiLife, v. 6.4.5. A discrepancy variable was calculated by subtracting objective sleep duration from subjective report of sleep duration on the Pittsburgh Sleep Quality Index, with negative values indicating underestimation and positive values indicating overestimation of objective sleep duration.
Results: More subjects who underestimated (88%) or overestimated (68%) the amount of sleep by an hour or more were in the BD group than the HC group, and more subjects who were accurate estimators were in the HC group (65%). Mean total sleep time did not differ between sleep discrepancy groups in HC. In contrast, mean total sleep time was 8.1 ± 1.0 for accurate estimators, 6.6 ± 1.0 h for underestimators, and 5.5 ± 1.6 for overestimators ($p < 0.01$) in BD. Both under- and overestimators had higher depression scores than accurate estimators ($p = 0.03$).
Conclusions: Sleep misperception is very common in BD, particularly the overestimation of sleep time. In those with BD who misperceived their sleep, sleep duration was shorter and depression was greater. Given that patients with BD report sleep disturbances both during and between mood episodes and that sleep disturbances predict impending episodes, objective measures of sleep should become part of their clinical assessment. Behavioral interventions for sleep disturbance in BD should be tailored to target sleep misperception.
Keywords: bipolar disorders, sleep
Disclosures: E. Saunders, Nothing to Disclose; S. Seaman, Nothing to Disclose; J. Fernandez-Mendoza, Nothing to Disclose; A. Jacobs, Nothing to Disclose; A. Gelenberg, Nothing to Disclose.

M214. The Clinical Relevance of Neural Network Dynamics for Bipolar Disorder

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Background: Functional magnetic resonance imaging (fMRI) has proved a powerful tool in examining disorder-related neural circuitry alterations in bipolar disorder (BD). Available evidence indicates abnormal recruitment and connectivity in circuits encompassing primary and associative perceptual regions, limbic and paralimbic structures (amygdala/hippocampus, anterior cingulate cortex) and ventral prefrontal cortical (VPFC) areas. These observations imply the involvement of large scale brain networks but do not provide any evidence of mechanisms relating these findings to clinical features of the disorder.
Methods: This study combined Statistical Parametric Mapping (SPM) with Dynamic Causal Modelling (DCM) to compare all plausible models of effective connectivity generated by fMRI data obtained during facial affect processing from euthymic patients with BD ($n = 47$) and matched healthy individuals ($n = 47$). DCM is a Bayesian model comparison procedure that models dynamic brain responses to external stimuli (e.g. facial visual stimuli) in terms of effective connections and their modulation by contextual factors (e.g. facial affect). Most importantly it allows the comparison of different models or families of models in terms of their evidence (that combines the goodness of fit with model complexity). The relative evidence for different models allows one to accommodate uncertainty about models when estimating connections strengths (that may correlate with clinical features), through Bayesian model averaging.
Results: There are two main findings. First, the most likely model of effective connectivity in patients was different from that of controls in terms of VPFC connectivity with the amygdala (increased) and the visual cortex in the inferior occipital gyrus (decreased). Second, healthy controls did not represent a unitary group; both diagnostic groups comprised heterogeneous populations of subjects whose data could be explained by a number of different models none of which had an exceedance probability (i.e. probability of one model being more likely than any other) above 40%. Therefore disease expression in BD may involve some mechanisms that deviate significantly from and others that are nested within the normal variation. This distinction is further supported by evidence that some connectivity models had unique clinical relevance. Specifically, data from patients with a history of rapid mood cycling were best explained by models of widespread increase in the effective connectivity of the amygdala within the face network.
Conclusions: We have shown that models of effective connectivity during facial affect processing capture the diversity in patients with BD. This approach allows us to delineate the clinical relevance of the different connectivity models seen in BD in terms of their associated clinical features. Facial affect processing does not represent the only avenue for defining biological mechanisms underpinning disease expression in BD. The decision to anchor this study on biological models of brain responses during affect processing was based on their face-validity and available support for the literature for facial affect processing abnormalities in BD.
Keywords: effective connectivity; dynamic causal modelling; neuroimaging
Disclosures: S. Frangou, Nothing to Disclose; D. Dima, Nothing to Disclose.

M215. Early Adverse Life Events: Interaction with Glucocorticoid [NR3C1] and Proinflammatory Cytokine [IL-1 β] Polymorphisms to Influence Gray Matter Variations in Females With and Without Chronic Abdominal Pain

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Background: Alterations in gray matter (GM) have been reported in patients with chronic visceral pain syndromes, including irritable bowel syndrome (IBS). Although such variations may be associated with clinical symptoms in patient populations, GM increases in the primary somato-

sensory cortex have also been reported in healthy subjects, where they are positively correlated with pain sensitivity, suggesting a possible role of genetic or epigenetic factors in determining such changes.

Aims: To evaluate the interactions of early environmental (EALs) and gene polymorphisms [glucocorticoids (NR3C1) and proinflammatory cytokines (IL-1β)] in influencing the cortical thickness (CT) of the subgenual anterior cingulate cortex (sgACC) in premenopausal female IBS patients.

Hypothesis: We hypothesized that the interaction between gene polymorphisms [glucocorticoids (NR3C1) and proinflammatory cytokines (IL-1β)] and early adverse life events (EALs) may play a role in shaping variations in grey matter (GM) thickness in a brain region of an emotional arousal circuit (sgACC), which has previously been shown to play a role in the affective modulation of sensory perception.

Methods: 527 individuals (223 irritable bowel syndrome patients [IBS], 304 healthy control subjects [HCs]) were genotyped for 2 SNPs of the NR3C1 gene (rs33389, rs2963155), and 1 SNP of the IL-β gene (rs16944). A subset of these subjects (210 female subjects [73 IBS]) completed structural MRI scans and differences in regional CT were determined by whole brain analysis. General linear models were constructed to examine the main and interactive effects of genetic variation with EAL, and diagnosis on CT of the sgACC, while controlling for race, age and total brain volume.

Results: No significant group differences in the prevalence of the 3 SNPs were detected. Significant main effects for EALs were demonstrated with greater EALs for IBS compared to HCs. IBS subjects as a group had significant reductions in cortical thickness (CT) in the left sgACC compared to HCs. Individuals (HC + IBS) homozygous for the most common NR3C1 haplotype had increased CT in the left sgACC compared to individuals with lesser common NR3C1 haplotypes regardless of EALs. However, a significant interaction between NR3C1 and IL-1β genotype and EALs was demonstrated. In individuals (HC and IBS) homozygous for the major IL-1β allele, the most common NR3C1 haplotype was associated with increased CT of the sgACC with increasing EALs while the least common NR3C1 haplotype was associated with decreased CT in the sgACC with increasing EALs. No effect of group on any of these interactions was observed.

Conclusions: The combined genetic variation in the NR3C1 gene and the IL-1β gene interacted with EALs to influence CT is the left sgACC. Even though no group differences in the frequency of these SNPs were observed, the greater prevalence of EALs in the IBS group may play a role in the observed reduction of sgACC CT in those patients, who had lesser common NR3C1 haplotypes, and were homozygous for the major IL-1β allele.

Keywords: early adverse life events, glucocorticoids, proinflammatory cytokines, cortical thickness, subgenual anterior cingulate cortex, chronic pain

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M216. Amygdalar Projections to Basilar Dendrites of mPFC Pyramidal Neurons Mediate CRF-Induced EPSCs That Are Enhanced by Ketamine

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Background: Corticotrophin releasing factor (CRF) has the dual role of activating the hypothalamic-pituitary-adrenal axis and extra-hypothalamic regions of the brain involved in the regulation behavioral responses to stress. Among the regions of brain expressing CRF receptors are the amygdala and mPFC (medial prefrontal cortex) whose reciprocal connections have been implicated in fear, anxiety, and depression (see Price and Drevets, 2010). Preliminarily, CRF was found to induce glutaminergic EPSCs in layer V pyramidal cells in rat mPFC brain slices; however, the inputs mediating these effects are unknown. One promising possibility is the basolateral nucleus of the amygdala (BLA), which strongly expresses CRF-1 receptors (Van Pett *et al*, 2000). In the BLA, pyramidal cells are selectively depolarized by CRF (Giesbrecht *et al*, 2010) and send projections to the basilar dendrites of layer V cells of the mPFC (Gabbott *et al*, 2012). Accordingly, we investigated whether CRF-induced EPSCs in mPFC depend upon the integrity of BLA inputs and whether such inputs are primarily to the basilar dendrites. For purposes of comparison, we tested 5-HT/serotonin- and hypocretin (hcrt)/orexin, which generate EPSCs mainly in apical dendrites (Liu and Aghajanian, 2008). In view of differences in dendritic field, we also tested whether the rapidly acting antidepressant ketamine, would enhance EPSCs

Methods: Whole cell patch clamp recordings were from mPFC layer V pyramidal cells in adult rat brain slices; responses to CRF (200 nM), 5-HT, and hypocretin were tested. Cells were filled with Neurobiotin and later imaged by 2-photon laser scanning. Excitotoxin lesions were made in the BLA; recordings were made after a lapse of two weeks to allow for degeneration of amygdalo-cortical projections. The apical dendritic tuft was severed in some layer V pyramidal cells to evaluate the relative contribution of apical versus basilar dendrites. Rapamycin (i.c.v.) pretreatment was used to determine if CRF-sensitive responses were enhanced by ketamine via the mTOR pathway.

Results: CRF induced an increase in EPSCs in mPFC layer V pyramidal cells displaying H-currents, a characteristic of cells that give rise to long subcortical projections (Gee *et al*, 2012). A second population (mainly thin-tufted cells lacking an H-current) had lesser responses to CRF. In all cases, EPSCs were blocked by CNQX, a selective AMPA receptor antagonist. Two weeks following excitotoxin lesions, CRH-induced EPSCs in layer V cells were reduced ~35%; this was associated with a decrease in basilar dendritic spine density. BLA lesions did not affect apically generated 5-HT- and hcrt-induced EPSCs. Disconnecting the apical turf did not interfere with the enhancement by ketamine of responses to CRF but markedly reduced its ability to enhance apically generated 5-HT and hcrt responses.

Conclusions: The lesion results show that BLA synaptic inputs to the basilar dendrites of mPFC layer V pyramidal cells are responsible for a significant fraction of CRF-

induced EPSCs; on the other hand, 5-HT- and hcrt-induced EPSCs, which are generated in the apical field, remain intact (Liu and Aghajanian, 2008). The converse dissociation between apical and basilar responses is known to occur after chronic stress: apical dendrites undergo atrophy resulting in a reduction of 5-HT and hcrt EPSC responses but basilar dendrites remain intact (Liu and Aghajanian, 2008). On the other hand, ketamine enhances EPSCs regardless of dendritic field. Given that basilar dendrites are spared by stress, we propose that CRF responses may similarly remain intact despite atrophy of apical dendrites; studies are underway to explore this possibility. If amygdala inputs to mPFC are preserved after chronic stress, this could create an imbalance between intact basilar and weakened apical inputs, possibly contributing to the hypothesized disproportionate influence of the amygdala in major depression. Price and Drevets (2010) Neuropsychopharmacology, 35:192–216 Van Pett, *et al.* (2000) J Comp. Neurol, 428, 191–212. Giesbrecht *et al.* (2010) J Neurosci, 30:16970–16982 Gabbott *et al.* (2012) J Comp Neurol, 520:2440–58. Liu and Aghajanian (2008) Proc Natl Acad Sci U S A, 105:359–64. Li *et al.* (2010) Science, 329 959–64. Gee *et al.* (2012) J Neurosci, 32:4959–71.

Keywords: major depression, dendritic spines, basilar dendrites, apical dendrites, layer v pyramidal cells

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M217. Identification of Signaling Cascades Regulating the Extinction and Reconsolidation of Cocaine-associated Memories Using Phosphoproteomics

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Background: Stimuli associated with drug use are powerful drivers of craving and relapse. Weakening these drug-associated memories through enhancing extinction and/or inhibiting reconsolidation with pharmacological agents have been proposed as potential treatments for addiction. However, in order to pharmacologically manipulate these specific memory processes, a better understanding of the signaling cascades that regulate extinction versus reconsolidation is required.

Methods: To identify the signaling networks that differentiate whether a memory undergoes extinction or reconsolidation, male Sprague-Dawley rats were trained to self-administer cocaine (1 mg/kg/infusion), with each infusion paired with a light + tone cue. Then, rats were placed in a novel context and the cocaine-paired cue was presented non-contingently either 3 times to reactivate the memory and induce reconsolidation or 120 times to produce extinction. A control group was placed in the novel context, but no cues were presented. Rats were euthanized 15 min later and the brains dissected, lysed, and subjected to tryptic digestion and enrichment for phosphopeptides by running through a TiO2 column. Samples from the amygdala were analyzed using unbiased, label-free quantitation using a nano-UPLC system coupled to an orbitrap mass spectrometer. A subset of the phosphopeptides identified in the discovery phase were further analyzed for quantitative differences using targeted, multiple reaction monitoring (MRM) mass spectrometry.

Results: Approximately 72 phosphopeptides were analyzed by MRM. Peptides were analyzed statistically if at least 4 out of the 5 transition states of the peptide could be detected and quantitated. The normalized average intensity across transitions for each phosphopeptide was computed for each sample and these values were averaged within groups. Group averages were compared statistically using an SRMstats restricted analysis and p-values corrected for multiple comparisons. Of the phosphopeptides analyzed, 10 did not display any significant regulation in the extinction or reconsolidation condition. Another 27 phosphopeptides were regulated in the same direction ($p < 0.1$) in both the extinction and reconsolidation condition, including subunits of the 60S ribosomal protein, supporting a role for protein synthesis in both memory processes. Finally, 35 phosphopeptides were specifically regulated by extinction only or reconsolidation only, with a small subset of those regulated in opposing directions between the two memory conditions. Examples of proteins differentially regulated by extinction and reconsolidation include Ca2 + /calmodulin dependent kinase II alpha (CaMKIIa), c-jun N-terminal kinase 3 (JNK3), and connexin 43. Overall, a signaling network involved in the regulation of microtubules and the actin cytoskeleton was modulated by these memory processes.

Conclusions: The results of these studies indicate that phosphoproteomics can be used to identify distinct signaling networks regulated by different memory conditions and implicates signaling cascades differentially regulating dendritic spine morphology in the reconsolidation and extinction of cocaine-associated memories. Finally, these studies have identified novel targets for addiction treatment development that can selectively modulate extinction or reconsolidation of the drug-associated memories that precipitate relapse.

Keywords: proteomics, extinction, reconsolidation, cocaine, self-administration

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M218. Role of a Beta-2 Adrenergic Receptor-regulated CRF-releasing Pathway from the BNST to the VTA in Stress-induced Relapse of Cocaine Use

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Background: Understanding the neurobiological pathways and mechanisms that underlie stress-induced relapse of cocaine use in recovering addicts is critical for the development of new and more effective strategies for the management of addiction. These studies investigated the role of a beta-2 adrenergic receptor (AR)-regulated CRF-releasing pathway from the bed nucleus of the stria

terminalis (BNST) to the ventral tegmental area (VTA) in stress-induced cocaine seeking using rat and mouse models of stress-induced relapse.
Methods: The mechanisms that mediate stress-induced cocaine seeking were assessed using a conditioned place preference (CPP-) based approach in mice and a self-administration (SA-) based approach in rats. In male C57BL/6 mice, reinstatement was examined following the extinction of cocaine-induced CPP established using a 15 mg/kg cocaine (ip) dose. In male Sprague-Dawley rats, reinstatement was examined following extinction after intravenous cocaine self-administration (14 × daily 2-h access to 1.0 mg/kg/inf cocaine).
Results: Using the mouse CPP approach, we found that beta-2 AR activation is both necessary for stress-induced reinstatement of extinguished CPP and sufficient to reinstate preference. The beta-2 AR-selective antagonist, ICI-118,551 (1 mg/kg, ip) prevented reinstatement by forced swim ($p < 0.05$ vs. veh) while administration of the beta-2 AR-selective agonist, clenbuterol (2 mg/kg) alone induced reinstatement ($p < 0.05$ vs. ext). Reinstatement by either forced swim or clenbuterol was attenuated by pretreatment with the CRF-R1 receptor antagonist, antalarmin (10 mg/kg, ip; $p < 0.05$ vs. veh), suggesting that CRF release and CRF-R1 receptor activation are downstream from beta-2 AR in the neural pathway that mediates stress-induced cocaine use. To further investigate the underlying neurocircuitry, we used a rat SA approach. Bilateral administration of the CRF-R1 receptor antagonist antalarmin into the VTA (500 ng/side) or the beta-2 AR antagonist ICI-118,551 into the BNST (0.25 nmol/side) prevented reinstatement by uncontrollable electric footshock (EFS; 15 min, 0.5 mA, 0.5 msec duration ave every 45 sec; $p < 0.05$ vs. veh), while delivery of CRF into the VTA (500 ng/side) or the beta-2 AR agonist clenbuterol into the BNST (5 μg/side) was sufficient to induce reinstatement of cocaine seeking ($p < 0.05$ vs. ext). To determine if a beta-2 AR regulated pathway from the BNST that releases CRF into the VTA is responsible for stress-induced reinstatement, we conducted a disconnection study in which ICI-118,551 (0.25 nmol) was unilaterally delivered into the BNST of one hemisphere and antalarmin (500 ng) delivered into the contralateral VTA prior to testing for stress-induced reinstatement. When administered into contralateral sites, this antagonist combination prevented EFS-induced reinstatement ($p < 0.05$ vs. veh + EFS). By contrast when the antagonists were administered into ipsilateral sites, EFS-induced reinstatement was unaffected. The ability of beta-AR receptor activation to induce cocaine seeking also requires CRF receptor activation in the BNST; intra-BNST anatalarmin (500 ng/side) delivery prevented reinstatement by intra-BNST clenbuterol. Last, we attempted to determine if CRF released into the VTA regulates cocaine seeking via processes that involve GABAergic or glutamatergic neurotransmission. Reinstatement by either EFS or intra-VTA CRF was not significantly reduced by $GABA_A$ receptor antagonist bicuculline (up to 10 μg/side). However, surprisingly both EFS- and CRF-induced reinstatement was blocked by intra-VTA administration of the $GABA_B$ receptor antagonist saclofen (3 μg/side). Intra-VTA kynurenic acid (24 μg/side) partially blocked EFS- and CRF-induced reinstatement but increased cocaine lever responding on its own, while the the NMDA receptor antagonist, AP-5 (up to 30 μg/side) or the AMPA receptor antagonist, NBQX (up to 10 μg/side) failed to block CRF- and EFS-induced reinstatement.
Conclusions: Altogether our data suggest that a key pathway from the BNST to the VTA mediates stress-induced relapse. This pathway is regulated by norepinephrine, in part via beta-2 AR, in the BNST and releases CRF into the VTA where it activates CRF-R1 receptors to induce cocaine seeking. In the VTA, the actions of CRF appear to involve an interaction with GABA and $GABA_B$ receptors while the precise contribution of glutamate is unclear and is likely complex. Understanding the processes through which stress promotes cocaine seeking should guide the development of treatments aimed at relapse prevention, particularly in cocaine addicts whose drug use is stress-related.
Keywords: stress relapse CRF norepinephrine VTA
Disclosures: J. Mantsch, **Part 1:** I am a co-founder of and consultant for Promentis Pharmaceuticals.; O. Vranjkovic, Nothing to Disclose; J. Blacktop, Nothing to Disclose.

M219. Brain Glucose Metabolism Predicts Fear Extinction Recall and Global Functioning in Trauma-exposed Populations With and Without PTSD

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Background: Following trauma exposure, a significant minority of individuals will develop posttraumatic stress disorder (PTSD). Tremendous scientific efforts have been deployed to study the brain regions and functions related to fear and extinction learning in individuals suffering from this disorder. It has been shown that various brain regions involved in the fear network have a greater resting state activity in PTSD than in trauma-exposed non-PTSD controls (TENC). In the same vein, individuals suffering from PTSD show intact capacity to acquire fear, but impaired ability to retain extinction learning. Studies in healthy humans have linked resting brain activity to fear extinction retention. However, there are no such studies in trauma-exposed individuals, and related findings could serve as an important resting state biomarker for PTSD. The goal of this study was to investigate whether brain glucose metabolism could be used to predict fear learning and extinction retention as well as general adjustment in individuals with a trauma history.
Methods: Twenty-four individuals meeting the diagnostic criteria for PTSD and twenty trauma exposed non-PTSD controls (TENC) were recruited. During their first visit, all participants had a diagnostic interview that included the global assessment of functioning (GAF) scale. During a second visit they were given a resting PET-FDG scan. Four days later, they underwent a well-validated two-day fear conditioning and extinction procedure in the fMRI scanner. Skin conductance responses (SCR) were measured and used as a proxy of fear levels. Resting glucose metabolism values were extracted for the following regions of interest: amygdala, hippocampus, dorsal anterior cingulate cortex (dACC) and ventromedial prefrontal cortex (vmPFC).

Resting metabolic ratios of vmPFC/dACC and vmPFC/amygdala were calculated and used as additional variables to predict fear learning.
Results: PTSD patients had higher resting brain metabolism in the amygdala and the hippocampus relative to the TENC group, replicating previous findings. Our results also replicated previous findings showing that both groups had similar fear learning, but that the PTSD individuals showed an impaired capacity to recall fear extinction on the second day. The vmPFC/amygdala resting metabolism ratio was significantly higher in TENC compared to PTSD. In addition, we performed correlations between resting brain metabolism values and fear levels as well as global functioning in the entire sample (combining PTSD and TENC groups). We found that the vmPFC/dACC resting metabolism ratio was negatively correlated with SCR during fear learning. In contrast, the vmPFC/amygdala ratio showed a positive association with extinction retention. Interestingly, resting brain metabolism in the amgydala and the hippocampus were negatively associated with scores on the GAF whereas vmPFC/amygdala ratio was positively associated with GAF. Lastly, a regression model found that GAF was significantly predicted by brain glucose metabolism, but only when all four ROIs and the two derived ratios were included in the statistical model.
Conclusions: In addition to replicating previous data demonstrating extinction retention deficits in PTSD, we showed that a greater vmPFC/dACC resting metabolism ratio was associated with lower fear levels during fear acquisition and that a greater vmPFC/amygdala resting metabolism ratio was associated with better fear extinction retention. Resting metabolism (amygdala, hippocampus and vmPFC/amygdala ratio) was predictive of the overall functioning of all participants. In addition, we showed that a global approach integrating multiple related regions could allow us to predict life functioning. Our data highlight the importance of a more integrative analytic approach to better understand global functioning and well-being of patients.
Keywords: PET Resting Metabolism, PTSD, Extinction Memory, Skin Conductance Responses, Global Assessment of Functioning
Disclosures: M. Marin, Nothing to Disclose; H. Song, Nothing to Disclose; L. Staples, Nothing to Disclose; M. VanElzakker, Nothing to Disclose; N. Lasko, Nothing to Disclose; R. Pitman, Nothing to Disclose; L. Shin, Nothing to Disclose; M. Milad, Nothing to Disclose.

M220. Imaging Amino Acid Neurotransmitter Responses to a Single Subanesthetic Dose of Ketamine in Major Depressive Disorder Using Proton Magnetic Resonance Spectroscopy

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Background: A major limitation of conventional antidepressant treatment of major depressive disorder (MDD) is the time lag in onset of benefit. A single subanesthetic dose of the glutamate-NMDA receptor antagonist ketamine, administered intravenously, has been reported to lead to remission within hours in many depressed patients, including those with treatment-resistant MDD. Animal model studies implicate glutamate- α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and downstream mammalian target of rapamycin (mTOR) signaling in this rapid antidepressant effect of ketamine. However, the mechanism by which ketamine activates glutamate-AMPA receptors and the mTOR pathway remains unclear. In this study of the mechanism of action of ketamine and its antidepressant effect in humans we used proton magnetic resonance spectroscopy (1 H MRS) to measure changes in glutamatergic compounds (glutamate + glutamine or Glx) and gamma-aminobutyric acid (GABA) following the intravenous administration of a single subanesthetic dose of ketamine to patients who were currently in a major depressive episode.
Methods: Eleven currently depressed DSM-IV MDD patients were enrolled in this pilot study. Levels of Glx and GABA in the medial prefrontal cortex (mPFC) were measured by 1 H MRS on a 3.0 T GE MR system using a standard J-editing technique, first at baseline and then dynamically every 13-min up to 90 min during and following a 40 min infusion of 0.5 mg/kg of ketamine. We monitored clinical outcome using the Profile of Mood States (POMS), a psychometric scale designed for rapid read-administration, and a modified Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI). Remission was defined as $<$ 10 point score and response as $>$ 50% improvement in HDRS-24 item version ($HDRS_{24}$) from baseline to several time points after ketamine administration.
Results: At 230 min after the start of ketamine infusion, 10/11 depressed subjects met criteria for remission. $HDRS_{24}$ scores improved by 88% (range 75–100%). mPFC Glx and GABA levels increased rapidly, peaking on average at 26 min at 37.8% and 38.0% above baseline, respectively. Clinical improvement and ketamine levels did not correlate with changes in mPFC Glx or GABA. However, concentration of serum norketamine, a highly active metabolite of ketamine, predicted clinical outcome at 90 min ($df = 6$; $r = -00.78$; $p = 0.023$).
Conclusions: This study is the first to report rapid and significant surges of MPFC Glx and GABA levels in patients with MDD *in vivo* following administration of a single dose of ketamine. A model is proposed for the rapid antidepressant mechanism of action of ketamine based on increased levels of these amino acid neurotransmitters and their effect on the AMPA/mTOR pathway.
Keywords: proton magnetic resonance spectroscopy, glutamate/glutamine (Glx), Major Depressive Disorder, gamma aminobutyric acid (GABA), AMPA/mTOR pathway
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educational grants and/or lecture fees from Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Otsuko, Pfizer, Sanofi-Aventis, and Shire. My family owns stock in Bristol Myers Squibb. ; R. Suckow, Nothing to Disclose; T. Cooper, Nothing to Disclose; D. Shungu, Nothing to Disclose; J. Mann, **Part 4:** I received prior unrelated grants from Novartis and GSK and receives royalties for commercial use of the C-SSRS from the Research Foundation for Mental Health.

M221. The Central Nucleus of the Amygdala Is Required for Habitual Cocaine Seeking through Functional Connectivity with the Dorsolateral Striatum

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Background: The transition from goal-directed to habitual drug seeking behavior depends upon progressive recruitment of dopamine circuitry that gradually shifts from more ventral and medial to more dorsal and lateral regions of the striatum. Thus, habitual drug seeking that is maintained at high rates by response-contingent presentations of these CSs depends upon dorsolateral striatal (DLS) dopamine transmission that is recruited by the core of the nucleus accumbens (NAcC). This habitual drug seeking is elicited and maintained by CSs that likely acquire their conditioned reinforcing properties (or incentive value) by associative processing in the basolateral amygdala (BLA), a region directly projecting to the NAcC, but not to the DLS. The BLA also projects to the central nucleus of the amygdala (CeN) which projects directly to substantia nigra (SNc) dopamine neurons that in turn innervate the DLS. Whereas the BLA is required for learning the pavlovian association of CS and US, the CeN – SNc—DLS circuitry may be a more important in maintenance of habitual cocaine seeking. We hypothesized that CeN inactivation would not influence goal-directed cocaine seeking, but would instead become progressively more important through its functional connectivity with the DLS and thereby control well-established or habitual seeking behavior.
Methods: Rats were implanted with two sets of bilateral cannulae targeting the CeN and the DLS and an indwelling intravenous catheter. They were then trained to self-administer cocaine (0.25 mg/infusion) under a FR1 schedule with infusions occurring in the presence of a 20-sec light CS. Following acquisition, the CeN was bilaterally inactivated via intracranial infusions using baclofen/muscimol cocktail (0.3/0.03 nmol/side) immediately prior to 15-min cocaine seeking test sessions in which each lever press was only reinforced by a 1-sec presentation of the CS [FI15(FR1:S)]. The response requirement was then gradually increased across sessions to a FI15(FR10:S) second-order schedule in which cocaine seeking was maintained over 15-min delays by 1-sec CS presentations on every tenth lever press. Cocaine seeking tests were again conducted. In a latin-square design, rats were challenged with the following sets of infusions: bilateral CeN baclofen/muscimol or vehicle; bilateral DLS α-flupenthixol (15 μg/side) or vehicle; unilateral CeN baclofen/muscimol combined with contralateral (unilateral) DLS α-flupenthixol (0, 10, and 15 μg/side); and unilateral CeN baclofen/muscimol combined with ipsilateral (unilateral) DLS α-flupenthixol (15 μg/side).
Results: Bilateral CeN inactivation had no effect on cocaine-seeking at the early-stage tests. Following extended training on the FI15(FR10:S) second order schedule, however, when high rates of behavior were maintained by contingent presentations of the drug-associated conditioned reinforcer, bilateral CeN inactivation disrupted cocaine-seeking to a level similar to that following bilateral DLS dopamine receptor blockade. Disconnection of the CeN and DLS achieved by unilateral inactivation of the CeN combined with DA receptor blockade in the contralateral DLS, resulted in a dose-dependent decrease in cocaine seeking, whereas double ipsilateral manipulations of the CeN and DLS had no effect, highlighting the functional impact of the disconnection.
Conclusions: The present study demonstrated that CeN processing is not required when cocaine seeking is goal-directed. Rather, the requirement for CeN-DLS functional connectivity in regulating cocaine seeking emerges as this behaviour becomes well-established and habitual. As such, we hypothesize that the incentive value assigned to the CS in the BLA early in training is routed via the CeN to influence the DLS control over habitual cocaine seeking following extensive training.
Keywords: conditioned reinforcement, habit, striatum, amygdala, incentive motivation
Disclosures: J. Murray, Nothing to Disclose; D. Belin, Nothing to Disclose; B. Everitt, Nothing to Disclose.

M222. Dopamine DREADDs: Chemicogenetic Control of VTA Dopamine Activity During Reinstatement of Cocaine Seeking

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Background: Ventral Tegmental Area (VTA) is a crucial brain substrate of motivated behavior, but the specific neurons that are involved in these processes are poorly understood. While VTA dopamine neurons are clearly involved in reward, a lack of specific tools to selectively manipulate dopamine neurons has previously limited our ability to test their specific functions in behaving animals.
Methods: 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 pharmacologically inert in the absence of DREADDs). DREADD-expressing neurons can therefore be experimentally controlled in a highly selective, 'lock-and-key' manner via modulation of endogenous G protein signaling pathways. DREADDs can be targeted to VTA dopamine neurons via local microinjections of viral vectors containing a floxed DREADD gene into transgenic rats, whose dopamine neurons express Cre recombinase (TH::Cre rats). This approach allows 'remote control' of dopamine neuron activity via systemic injections of CNO. Here, we use viral vectors to express excitatory or inhibitory DREADDs (Gs, Gq, and Gi-coupled) bilaterally in VTA dopamine neurons of TH::Cre transgenic rats. We examined

effects of inhibiting or exciting these dopamine neurons on cue-induced, cocaine-primed, and pharmacological stress (yohimbine)-induced reinstatement of cocaine seeking, as well as behavioral economic measures of cocaine motivation and value. We also examined effects on cocaine seeking behavior of contralaterally disconnecting VTA dopamine neurons from their dense, reinstatement-related inputs from ventral pallidum (VP).
Results: DREADD-based stimulation or inhibition of VTA dopamine neurons differentially modulated cocaine seeking in all three types of reinstatement. In addition, contralateral disconnection of VTA dopamine neurons from VP robustly attenuated cue-induced and cocaine-primed reinstatement, suggesting that VP connectivity with VTA dopamine populations is a crucial pathway mediating cocaine seeking.
Conclusions: These results confirm an important role for VTA dopamine neurons in cocaine seeking, and show that stimulation of different G protein-coupled signaling pathways in these neurons results in distinct behavioral phenotypes. We also show that communication between VTA dopamine neurons and their VP afferents is required for reinstatement of cocaine seeking. These findings show that VTA dopamine-containing neurons are crucially involved in wider circuits mediating reinstatement of cocaine seeking in rats, and therefore are potentially involved in relapse to drug use in human addicts.
Keywords: VTA, dopamine, DREADDs, reinstatement, cocaine
Disclosures: S. Mahler, Nothing to Disclose; B. Cox, Nothing to Disclose; G. Aston-Jones, Nothing to Disclose.

M223. Dorsal and Ventral Prefrontal Neuronal Activity and Cocaine Seeking: More Complex than Thought

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Background: Previous research has demonstrated a critical role for the prefrontal cortex in driving and regulating drug seeking. In the rodent, subdivisions of the medial prefrontal cortex (mPFC) appear to play different roles in this behavior. The dorsal prelimbic cortex (PL) has been hypothesized to promote execution of cocaine seeking whereas the ventral infralimbic cortex (IL) has been shown to regulate extinction of cocaine seeking. The absolute nature of this dichotomy has been challenged recently by studies showing an important role for PL in inhibiting cocaine seeking when circumstances necessitate inhibition. In addition, studies of other drugs of abuse have demonstrated a more complex relationship between mPFC subdivisions and seeking/extinction. Recent research from our laboratory has shown that PL and IL neurons play complex roles in seeking of and extinction learning related to natural rewards, with each region signaling aspects of context and learning throughout the study. These findings argue that a detailed interrogation of PL and IL neuronal activity during drug seeking is important in understanding the relationships of these areas to different aspects of drug-related behavior.
Methods: Here we investigated the activity of multiple single neurons during self-administration, extinction, and cue- and drug-induced reinstatement of cocaine-seeking. Sprague Dawley male rats were trained to press an active lever for intravenous cocaine (FR1; 0.2 mg/50 μL infusion; 20-s TO; 2-hr sessions) and a discrete tone-light cue. Presses on the inactive lever were recorded but produced no outcome. After two weeks of stable FR1 (>10 presses/session), animals were tested in a combined extinction (EXT)/FR1 session (1-hr each). Animals then underwent EXT sessions in which lever presses were recorded but produced no outcome. Following at least two days of extinguished behavior (<10 presses/session) animals underwent cue-induced reinstatement sessions in which active lever-presses produced tone-light cues but no delivery of cocaine. Finally, a subset of animals underwent cocaine-induced reinstatement where an IP injection of cocaine (10 mg/kg) drove lever pressing in the absence of cues or cocaine infusions. Single-neuron recordings were made from microwire arrays implanted bilaterally in prelimbic (PL) and infralimbic (IL) areas of the mPFC during each of the behavioral stages (FR1, EXT/FR1, EXT, cue-reinstatement, coc-reinstatement).
Results: Neurons in both PL and IL ($n > 100$ in each region at each task stage) were strongly driven during all stages of task performance. During FR1, both PL and IL neurons signaled approach to lever-press, lever-press, cues, and cocaine infusions. In addition, neurons in both PL and IL exhibited session-long tonic modulation, often combined with phasic event-locked responses. Similar profiles of responses were observed in each of the latter stages of testing. The number of responsive neurons (both event-locked and session-long) decreased across extinction and was strongly upregulated during cue- and, to a lesser extent, cocaine-induced reinstatement. Differences were seen in PL and IL neuronal responses, in some cases supporting previous characterization of these regions in drug seeking. Significantly modulated PL and IL neurons exhibited complex, but opposing firing patterns during cocaine self-administration. Additionally, PL neurons fired more robustly than IL neurons during reinstatement. However, both PL and IL neurons exhibited robust modulation in all phases of the study, arguing against a direct relationship between PL/IL and seeking/extinction.
Conclusions: Despite some alignment with previous results (e.g., PL driving reinstatement of cocaine seeking), differences were more complex than simply signaling drug-seeking vs. extinction. These data indicate that both PL and IL neurons play multifaceted roles in execution and inhibition of drug-seeking behaviors. Rather than specific behavioral functions being mapped onto specific brain areas, circuits within mPFC subregions likely contribute to diverse and overlapping behaviors. Understanding how these networks interact during drug seeking and extinction will refine our conceptualization of these behaviors and will facilitate more precise identification of treatment targets.
Keywords: prefrontal behavioral electrophysiology cocaine extinction reinstatement
Disclosures: D. Moorman, Nothing to Disclose; G. Aston-Jones, Nothing to Disclose.

M224. Cytokine and Chemokine Profiling of Plasma and CSF Identifies the MCP-4/MCP-1 Ratio as a Novel Candidate Plasma Biomarker for Chronic Post-Traumatic Stress Disorder

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Background: Post-traumatic stress disorder (PTSD) is psychiatric disorder, which occurs following exposure to traumatic events. PTSD may be acute or chronic, and can have a waxing and waning course of symptoms. It has been hypothesized that proinflammatory cytokines and chemokines in the CSF or plasma might be biomarkers, surrogates, or drivers for the psychophysiological mechanisms relating a history of trauma exposure to changes in behavior and mental health disorders and medical morbidity. However, in a carefully controlled study of CSF from a small hippocampus cohort of civilian PTSD patients, all free from Major Depressive Disorder (MDD), concentrations of Corticotrophin Releasing Factor (CRF), IL-6, BDNF, IGF-1 and Substance P were found to be identical to levels in CSF found in normal controls (Bonne *et al*, 2011).
Methods: Here, we further test the cytokine/chemokine hypothesis for PTSD by examining levels of 16 classical cytokines and chemokines in CSF, sampled at 9 AM, and plasma sampled at the 2 AM and 9 AM time points. We also test whether paroxetine® affects these levels in a subset of the PTSD cohort. The PTSD and healthy control patients are all from the PTSD and Healthy Control cohort, with few comorbidities, initially described by Bonne *et al* (2011). We quantitatively measured cytokines and chemokines using a multiplexed electrochemiluminescent ELISA platform.
Results: We find that in plasma, collected at either 2 AM or 9 AM, the MCP4/MCP1 *ratio* significantly discriminates between PTSD ($N=14$) and Healthy Control ($N=10$) patients. At the 9 AM time point, the MCP-4/MCP-1 ratio in PTSD plasma is elevated 66% ($p=0.004$; $AUC=0.84$). In CSF, collected at 9 AM from the same patients, we find that the MCP-4/MCP-1 ratio is not informative. However, the levels of IL-8 in 9 AM CSF trend lower in PTSD patients compared to Healthy Controls (reduced by *ca*. 25%, $p=0.06$). Finally, following eight weeks of therapy with paroxitine®, there were no effects on any of the individual analytes, or on the MCP-4/MCP-1 ratio in the plasma collected at 9 AM following 8 weeks of therapy.
Conclusions: These data suggest that the MCP-4/MCP-1 ratio in plasma is a candidate biomarker for PTSD. It remains to be discovered whether the set points for MCP-4 or MCP-1 concentrations in PTSD plasma have a relationship to intrinsic behavioral or structural deficits in the PTSD brain, and whether either of these chemokines might also be candidate targets for therapy.
Keywords: PTSD, cytokines, chemokines, MCP-1, MCP-4, biomarker, plasma, CSF
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M225. Biomarkers Differentiating Major Depressive Disorder Subtypes

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Background: The identification of molecular biomarkers for major depressive disorder (MDD), compared with other diseases has yielded few reproducible results. One hypothesis for the inconsistent performance of biomarkers is that MDD is comprised of a biologically heterogeneous set of diseases. Further, the search for biomarkers is complicated by limited access to directly relevant (i.e. brain) tissues. To overcome these challenges, in this study, we use molecular data derived from blood to differentiate among symptomatically defined depression subtypes. Blood-based biomarkers which reflect different patient subpopulations would have a positive impact on treatment through better understanding of molecular mechanisms contributing to depression, selection of subjects suitable for a specific clinical trial, and the identification of therapeutic interventions optimal for a depression subtype.
Methods: Blood samples were collected from 100 healthy control subjects and 100 unmedicated depressed subjects (HAMD-17 $>=$ 18). Melancholic depression was assessed using CORE (CORE $>=$ (8), and anxious depression by the MINI (number of comorbid anxiety disorders $>$ 0). Samples were analyzed using transcriptomic (Affymetrix, HGU133 Plus 2.0) and metabolomic (Metanomics Health) technologies. Resulting datasets were analyzed using multiple machine learning algorithms for classification and feature selection in order to identify biomarkers which best separated depressed subjects from healthy controls. For pathway analysis, clusters of metabolites with similar expression were used to classify melancholic depression from healthy controls. This method retains features which are often part of the same pathway, but might be discarded as redundant information during biomarker selection. Pathway and network analysis was performed using top differentiating metabolomic clusters to identify molecular pathways which are altered in melancholic depression.
Results: Melancholic and anxious depression subtypes were classified with better accuracy than MDD as a whole using either metabolomic or transcriptomic features. Metabolomic data showed better classification accuracy than transcriptomic datasets. Best performance was achieved using metabolite data in melancholic depression, with an accuracy of around 80%. Analysis of metabolites differentiating melancholic depression identified pathways involving well-characterized metabolites such as serotonin and dopamine. Network analysis revealed affected classes of molecules such as amino acids (10 amino acids with

1.4–2.0-fold increase in melancholic depression), and metabolites associated with stress and the suppression of inflammation (4 corticosterone-related metabolites increased 1.2–1.4-fold in melancholic depression) were also present.
Conclusions: Dividing MDD subjects into melancholic and anxious depression subtypes resulted in improved classification performance over MDD as a whole. These results support the hypothesis that MDD may be comprised of multiple biological diseases, and these may be distinguishable using molecular biomarkers from blood.
Keywords: Molecular Biomarkers depressive melancholic anxious depression
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M226. Contribution of a Mesocorticolimbic Subcircuit to Drug Context-induced Reinstatement of Cocaine-seeking Behavior in Rats

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Background: Cocaine-seeking behavior triggered by drug-paired environmental context exposure is dependent on orbitofrontal cortex (OFC) - basolateral amygdala (BLA) interactions.However, the larger neural circuitry within which the OFC and BLA interact to promote drug context-induced goal-directed behaviors remains to be investigated. Emerging evidence suggests that dopaminergic neurotransmission in the OFC may be necessary for a drug-paired context to produce cocaine-seeking behavior. Thus, we hypothesized that input from the ventral tegmental area (VTA) to the OFC—via dopamine D1-like receptor stimulation—regulates interactions between the OFC and BLA that promote the motivational effects of cocaine-paired environmental stimuli on drug-seeking behavior.
Methods: To test this hypothesis, in experiment 1, we examined the effects of bilateral SCH23390 (0.02 or 0.2 μg/hemisphere), a dopamine D1-like receptor antagonist, in the OFC and in the adjacent primary/secondary motor cortex (M1/2, anatomical control region) on drug context-induced cocaine-seeking behavior and on indices of instrumental and general motor performance. We confirmed the receptor specificity of SCH23390 effects on cocaine-seeking behavior by co-administering SKF81297 (0.1 or 0.3 μg/hemisphere), a dopamine D1-like receptor agonist. In experiment 2, we evaluated the effects of VTA-OFC-BLA functional disconnection and control manipulations on drug context-induced cocaine seeking. Specifically, to bilaterally disrupt intrahemispheric neural communication, rats received unilateral SCH23390 (0.2 μg) pretreatment into the OFC *plus* unilateral $GABA_B/GABA_A$ receptor agonist cocktail, baclofen + muscimol (BM; 106.8/5.7 ng), pretreatment into the contralateral BLA. To bilaterally disrupt interhemispheric communication, additional rats received the same pretreatments ipsilaterally. The same rats were also tested following contralateral or ipsilateral VEH pretreatment. Additional control groups were tested following unilateral SCH23390 or VEH pretreatment into the OFC or unilateral BM or VEH pretreatment into the BLA . Functional interdependence within the VTA-OFC-BLA circuit was predicted to manifest as a superadditive effect following contralateral or ipsilateral manipulation relative to the additive effects of separate, unilateral manipulation of each target brain region. Finally, in experiment 3, we verified that the requisite anatomical connections are in place to support the proposed VTA-OFC-BLA neural circuit. To this end, we used fluorescent retrograde tracers, Red Retrobeads™ and Green Retrobeads™ to label and qualitatively compared the relative density of monosynaptic projections from the VTA and substantia nigra (SN) to the OFC and between the BLA and OFC.
Results: In experiment 1, intra-OFC, but not intra M1/2, pretreatment with the dopamine D1-like receptor antagonist, SCH23390, dose-dependently attenuated cocaine-seeking behavior ($p < 0.05$), without altering motor performance.

Furthermore, the effects of SCH23390 could be surmounted by co-administration of a sub-threshold dose of the D1-like receptor agonist, SKF81297. In experiment 2, unilateral SCH23390 administration into the OFC plus GABA agonist-induced neural inactivation of the contralateral or ipsilateral BLA disrupted drug context-induced cocaine-seeking behavior relative to vehicle ($p<0.05$), while independent unilateral manipulations of these brain regions were without effect. Lastly, in experiment 3, the distribution pattern of the fluorescent retrobeads indicated that the VTA, but not the SN, sends dense intra- and interhemispheric projections to the OFC, which in turn has reciprocal bi-hemispheric connections with the BLA.

Conclusions: These findings support that dopaminergic input from the VTA, via dopamine D1-like receptor stimulation in the OFC, regulates intra- and interhemispheric interactions between the OFC and BLA that promote drug context-induced cocaine seeking. Thus, a VTA-OFC-BLA neural circuit promotes drug context-induced motivated behavior. From an addiction treatment perspective, it will be important to systematically identify the brain regions with which the newly characterized VTA-OFC-BLA circuit interacts. Complementing this approach, future studies will need to characterize putative drug-induced and experience-based neuroadaptations within the circuitry that enhance cue reactivity and the propensity for cue-induced relapse in substance abusers.

Keywords: relapse, cocaine, dopamine, orbitofrontal cortex, amygdala, ventral tegmental area

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M227. The Involvement of the Serotonergic System in the Nucleus Accumbens Shell on EtOH-Seeking: Role of 5HT7 Receptors and Response to Conditioned Cues

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Background: Conditioned drug cues contribute significantly to drug craving and increase the likelihood that an individual will relapse. Recent data from our laboratory show that odor cues that signal access to or the absence of alcohol differentially alter cFos expression and DA levels within the nucleus accumbens shell (AcbSh), a neurological substrate for drug reward. There is evidence that 5-HT_7 receptors in the AcbSh are involved in the regulation of self-control/behavioral inhibition as microinjections of a 5-HT_7 receptor agonist increased and microinjections of an antagonist decreased behavioral self-control.

Methods: The first series of experiments examined the effects of 5-HT_7 receptor agents on context-induced EtOH-seeking (spontaneous recovery). The 5-HT_7 receptor antagonist SB269970 was microinjected (0, 0.1, 1, and 10 μM/side) into the AcbSh or the nucleus accumbens core (AcbC) prior to EtOH-seeking testing. In additional subjects, the 5-HT_7 receptor agonist LP-12 was microinjected (0, 25, and 100 μM/side) into the AcbSh prior to EtOH-seeking testing. To determine the effects of conditioned cues on serotonin levels within the AcbSh was conducted using excitatory, inhibitory, and neutral odor cues. For 10 consecutive daily sessions, alcohol-preferring (P) rats self-administer 15% EtOH or water in the presence of an olfactory cue (CS+). On days 71–77, P rats were given daily operant sessions with EtOH and water unavailable in the presence of a 2nd odor cue (CS-). From days 58–77, all rats were exposed to a 3rd odor in a non-drug paired environment for 1 h (exposure occurred at least 2 h separated from operant testing). Rats were implanted with guide cannuale aimed at the AcbSh on day 84. Microdialysis was performed on day 91 in a non drug-paired environment (animals were habituated to this environment). Standard microdialysis procedures were used; samples were collected every 8 min, and rats were exposed to the CS+, CS−, or CS^0 for a total of 24 min.

Results: Microinjection of the 5-HT_7 receptor antagonist SB269970 into the AcbSh, but not AcbC, enhanced EtOH-seeking in the P rat. In contrast, microinjection of the 5-HT_7 receptor agonist LP-12 into the AcbSh blocked the expression of EtOH-seeking. Exposure to the CS+ produced a rapid, pronounced reduction in 5HT levels in the AcbSh for the 24 min period of odor exposure (55–64% reduction for all 3 samples takend during odor exposure). Exposure to the CS− or CS^0 did not alter 5HT levels in the AcbSh.

Conclusions: The data indicate that altering the activity of the 5-HT_7 receptor within the AcbSh has a bi-directional effect on EtOH-seeking in P rats. The data also indicate that the neurochemical effects of presenting a CS+ (reduction in 5HT levels in the AcbSh) are complementary to the pharmacological data. Thus, the inhibition of 5-HT release within the AcbSh may represent an underlying neurological mechanism contributing to both EtOH-seeking and conditioned cue enhancement of EtOH-seeking.

Keywords: Craving, Serotonin, Accumbens, pharmacology, neurochemistry

Disclosures: G. Deehan, Nothing to Disclose; S. Hauser, Nothing to Disclose; E. Engleman, ; J. Wilden, ; W. Truitt, ; W. McBride, ; Z. Rodd,

M228. Maltreated Preschoolers: The Association of Stress Exposure with Adrenocortical and Behavioral Outcomes

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Background: Childhood adversity is a significant risk factor for the development of depressive and anxiety disorders. The HPA axis, a major coordinator of the physiologic response to stress, functions abnormally in individuals with a history of significant early stress, though few studies have examined this relationship in preschool-aged children. Initially, research was focused on hyperactivity of this axis and showed associations with early stress and with

depressive disorders. However, several studies have now shown that maltreated preschool-aged foster children have blunted diurnal cortisol concentrations in comparison to matched controls (Bruce *et al*. 2008; Fisher *et al*. 2007; Dozier *et al*. 2006). Similarly, a limited amount of work has examined HPA axis activity relative to depressive or anxiety symptoms in preschool-aged children. Two studies have linked psychopathology in preschoolers to elevated cortisol levels in response to a challenge task (Luby *et al*. 2003; Hatzinger *et al*. 2012). In contrast, one study showed that preschool-aged children with depressive symptoms exhibited an attenuated cortisol response to a psychosocial stressor. This is an initial report from the first 100 families in a longitudinal study of biomarkers of risk and resilience in maltreated and non-maltreated preschool-aged children. We hypothesized that chronic stress exposure would be associated with blunted cortisol concentrations and that stress exposure and blunted cortisol levels would be linked to symptoms of depression and PTSD.

Methods: Families were recruited through the state child welfare agency with an indicated case of maltreatment of moderate or higher severity ($n = 35$) and through a pediatric clinic serving low income families ($n = 65$). Children between 3–6 years of age were eligible ($M = 4.16$, $SD = 0.70$). Almost all families were receiving public assistance. There were 45 boys and 55 girls; 32 white and 68 non-white children. Biological mothers completed the Diagnostic Infant and Preschool Assessment (DIPA) PTSD, depression, separation anxiety, and reactive attachment disorder modules; the Child Behavior Checklist (CBCL) total, internalizing, and externalizing scales; a series of questions regarding chronic family stressors, as well as traumatic experiences. The children provided 4 samples of saliva for determination of cortisol levels during a laboratory stressor home visit, as well as 3 days of saliva for determination of diurnal cortisol.

Results: The number of chronic stressors was associated with lower AM cortisol concentrations (Spearman $\text{rho} = -0.27$, $p < 0.01$) as well as the diurnal change in cortisol over the day ($\text{rho} = -0.298$, $p < 0.005$). Neither maltreatment group nor number of traumas was associated with cortisol and the home visit cortisol samples were not correlated with any of the stress measures. Depressive symptoms were negatively correlated with AM and PM cortisol ($\text{rho} = -0.24$, $p < 0.05$) and there was a trend for negative correlation with bedtime cortisol ($\text{rho} = -0.23$, $p < 0.05$). Depressive symptoms were negatively correlated with pre-arrival home visit cortisol ($\text{rho} = -0.21$, $p < 0.05$) and also with decline in home visit cortisol ($\text{rho} = 0.20$, $p < 0.05$).

Conclusions: These findings suggest that recent stress exposure may lead to blunted awakening cortisol levels in at-risk children, and that attenuated diurnal cortisol is linked to depressive symptoms as early as preschool age in children from socioeconomically-disadvantaged families. Future work in this study will expand the number of maltreated and non-maltreated children, examine the effects of stress exposure timing and severity, examine effects of candidate risk genes on risk and resilience and test the hypothesis that cortisol mediates these effects, determine whether stress exposure is linked to epigenetic changes and telomere shortening, and examine longitudinal effects of biomarkers, as well as behavior and symptoms.

Keywords: stress childhood maltreatment cortisol depression ptsd risk poverty

Disclosures: A. Tyrka, Nothing to Disclose; S. Parade, Nothing to Disclose; N. Eslinger, Nothing to Disclose; B. Shillan, Nothing to Disclose; A. Clement, Nothing to Disclose; R. Berger, Nothing to Disclose; S. Dickstein, Nothing to Disclose; R. Seifer, Nothing to Disclose.

M229. Contributions of Ventral Dopamine Target Neurons to Risk-seeking Decisions in a Macaque Model of Compulsive Gambling

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Background: Like drug addiction, compulsive gambling results in patterns of costly behavior despite efforts to abstain. Rational development of treatments can benefit greatly from delineation of neural processes that determine risk-seeking decisions. The most detailed models require an understanding of single neuron responses; these are most practically obtained in animal models. Although animals are almost universally risk-averse, we have recently developed a novel training regimen and task that promote persistent risk-seeking in rhesus monkeys. Like pathological gambling in humans, these risk-seeking behaviors in monkeys are self-reinforcing and resistant to extinction. Compulsive behavior is thought to result in part from aberrant plasticity induced by dopamine release into its target regions. Two of the most prominent dopamine targets are the ventral striatum (VS) and the ventromedial prefrontal cortex (vmPFC), both brain areas that are strongly implicated in both addiction and choices about rewards. Although neuroimaging and lesion studies demonstrate the key importance of these areas in driving reward decisions, including risky ones, the specific contributions of these areas remains unclear.

Methods: We used standard single-unit methods to record responses of single neurons in the ventral striatum (targeting the accumbens core region) and (in separate sessions) the ventromedial prefrontal cortex (area 14) while monkeys performed a novel gambling task. The task requires monkeys to choose between two risky options that differ in probability of a reward and size of reward offered on each trial. We have previously established that this task induces costly and habitual risk-seeking behavior, and that it has some face validity for compulsive gambling (Heilbronner and Hayden, Frontiers Decision Neuroscience, 2013). All rewards were aliquots of water delivered orally. Monkeys performed 500–2000 trials per session. A key element of our task is that offers are staggered in time (i.e. asynchronous) by 1 second, allowing us to assess neuronal representations of offers themselves.

Results: Both monkeys were highly risk-seeking, choosing to gamble even when it was costly in both the short and long term. We found that both vmPFC and VS neurons exhibited a clear and consistent pattern of responses implicating them in reward-based decisions. Specifically, neurons represented, in sequence, the value of the two options, the

difference between them, the value of the chosen option, and (following the resolution of the gamble) the value of the obtained option, a signal that persisted well into the next trial. These results link both areas to representation and comparison of values and to monitoring of the consequences of choices. Unlike dopamine neurons, which carry reward prediction error signals, neurons in these dopamine targets tracked offered values regardless of prediction (i.e. expectancy signals). We also found weak but significant spatial tuning for offer position and for choice, suggesting that these areas may contribute to the assignment of values to actions. Finally, we found that neurons represent subjective values, rather than mathematically defined expected values. Because subjective values are determined by choices, thee results link responses to choices. We found qualitatively similar patterns of responses in VS and vmPFC. However, VS signals were substantially larger, more prevalent, and more task-aligned. Nonetheless, we found some evidence that vmPFC stores a memory trace during the delay between options that is absent in VS.

Conclusions: Ultimately, our finding that preferred high-risk options are associated with stronger representations in both regions is consistent with the idea that risk-seeking observed in compulsive gambling reflects undue weight placed on these options in the valuation process that precedes the decision to gamble. Moreover, we provide the first evidence that vmPFC and VS—two major targets of the dopamine system—participate in representation of offered and received rewards, and that they participate in comparison of offers. Neurons in both areas during the comparison period reflect the difference in values for the two options, suggesting that they may compare values using a mutual inhibition process. If so, this would suggest that value comparison occurs through the same mechanisms as perceptual comparisons.

Keywords: compulsive gambling, risk, ventral striatum, ventromedial prefrontal cortex, macaque

Disclosures: B. Sleezer, Nothing to Disclose; B. Hayden, Nothing to Disclose.

M230. Frontal and Subcortical Pathways Provide a Basis for Segmenting the Cingulum Bundle: Implications for Understanding the Default Mode Network, Diffusion Imaging, and Surgical Targets for Psychiatric Disorders

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Background: The cingulum bundle (CB) is one of the brain's major fiber pathways, running from the medial frontal lobe through the parietal and temporal cortices. It connects the medial prefrontal cortex and the posteromedial cortex, two important areas within the default mode network (DMN), a set of brain regions that are highly active at rest. Diffusion magnetic resonance imaging (dMRI) shows that specific areas within the CB are abnormal in psychiatric disorders, including major depressive disorder (MDD) and obsessive-compulsive disorder (OCD). Intriguingly, the CB is also a target for ablative neurosurgical treatment (cingulotomy) for these disorders, as well as deep brain stimulation (DBS) for MDD. The goal of these studies was to identify the organization of the CB and how different cortical and subcortical structures use this bundle to reach their targets. The results provide new insights for interpreting surgical targets for OCD and MDD and abnormalities in white matter associated with those diseases.

Methods: Using tracer injections in different subcortical, cingulate, and non-cingulate frontal targets in monkeys, we mapped efferent fiber pathways through the CB. We also used immunocytochemistry for antibodies directed against tyrosine hydroxylase (TH) and serotonin transporter (SERT), to visualize TH and SERT-positive fibers through the CB. To determine fibers likely involved in cingulotomies and subcallosal DBS, we transformed the lesion and DBS electrode locations to fit the monkey brain and checked placement based on landmarks.

Results: Based on cortical and subcortical projection systems, the CB can be segmented into four distinct regions: rostral subgenual, rostral dorsal, caudal dorsal, and temporal regions. TH and SERT-positive, posterior cingulate, and nucleus basalis fibers travel through all four of these zones. In contrast, frontal fibers (anterior cingulate, orbitofrontal, dorsolateral, and dorsomedial cortices) have a more restricted projection pattern: they do not use the temporal CB. Amygdala fibers do project through the temporal CB, but not the caudal dorsal CB. Finally, anteroventral thalamus, orbital proisocortex, and pre-SMA fibers are absent from the subgenual CB. The cingulotomy lesion spans portions of the rostral dorsal and caudal dorsal segments of the CB. Thus, it will likely ablate all cingulate, non-cingulate frontal cortical, and subcortical fibers passing through the CB. Importantly, this will include frontal reciprocal connections to posteromedial cortex. In addition, a cingulotomy will disrupt frontal and posterior cingulate fibers that travel to the dorsomedial cortex, including areas 9, 8, 6, and 7 M. Specific subcortical fiber projections will also be interrupted, including serotonergic, dopaminergic, and nucleus basalis projections to caudal dACC, dorsomedial cortex, and posteromedial cortex. Interestingly, the cingulotomy lesion is in one of the only locations in the bundle containing both anteroventral thalamic and amygdala fibers. More rostral lesions will be more likely to affect amygdala projections, and less likely to affect anteroventral thalamic projections, while more caudal ones will likely affect thalamic but not amygdala fibers. Subcallosal DBS for MDD will involve the caudal portion of the subgenual CB. Stimulation will capture a number of subcortical (nucleus basalis, amygdala, dopaminergic, serotonergic) pathways. These fibers travel to the rostral dorsal CB via the subgenual CB. While cingulate and prefrontal fibers terminating in caudal subgenual cingulate will be in the path of stimulation, those projecting through the dorsal CB will not be. Importantly, this target will not involve anteroventral thalamus fibers.

Conclusions: On the basis of frontal cortical, cingulate, and subcortical projections through the CB, the bundle can be divided into four distinct zones: subgenual, rostral dorsal, caudal dorsal, and temporal. Prior studies show that specific subparts of the CB are abnormal in psychiatric disorders. For example, fractional anisotropy of the subgenual CB is reduced in those vulnerable to MDD (Keedwell *et al*, 2012). This region connects specific cortical and subcortical

regions, but not others. Thus, by segmenting the CB, we can determine the specific connections associated with psychiatric white matter abnormalities. Segmentation also provides a guide for interpreting neuro-therapeutic approaches such as cingulotomy and subcallosal DBS. For example, the CB is the main link between the two main regions of the DMN, the posteromedial cortex and the medial prefrontal cortex. These are spatially separate, yet functionally linked, areas. Observations indicate that a cingulotomy lesion will sever *all* of the direct links between these two DMN areas. Finally our results have the potential to shed light on the relationship between DMN activity, the CB, and psychiatric disorders.

Keedwell, P.A., Chapman, R., Christiansen, K., Richardson, H., Evans, J., and Jones, D.K. (2012). Cingulum white matter in young women at risk of depression: the effect of family history and anhedonia. Biol Psychiatry *72*, 296–302.

Keywords: OCD, depression, white matter, diffusion MRI, deep brain stimulation, default mode network

Disclosures: S. Heilbronner, Nothing to Disclose; S. Haber, Nothing to Disclose.

M231. Rules Prefrontal Pathways Use in the Anterior Limb of the Internal Capsule: Implications for Neuroimaging and Deep Brain Stimulation

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Background: The anterior limb of the internal capsule (ALIC) is one of the brain's major projection tracts, connecting cognitive control areas in the prefrontal cortex (PFC) with thalamic and subcortical regions. ALIC abnormalities, in both volume and diffusion imaging parameters are associated with several psychiatric disorders, including schizophrenia, obsessive-compulsive disorder (OCD), depression (MDD), and addiction. Thus, the ALIC is of substantial interest for neuroimaging, psychiatry and neurosurgery research, and is a target site for Deep Brain Stimulation (DBS) therapy for OCD and MDD. We previously demonstrated specific rules that determine the fiber position from different ventral prefrontal areas within the ALIC (Lehman *et al*. '11). Importantly, we also showed that these organizational principles found in non-human primates are preserved in humans (Jbadi *et al*, '13). The goal of this study was to understand the rules that govern the fiber trajectories through the ALIC from the entire of PFC and to determine the likely fibers involved in DBS.

Methods: Tracers were injected to different PFC regions. We combined conventional anatomical charting methods with computerized 3D modeling delineated the efferent trajectories of fibers from different locations in the PFC (Lehman *et al*, 2011). To determine the specific pathways involved at the different DBS VC/VS contacts, we scaled the DBS electrode to fit the monkey brain.

Results: The results identify the paths taken by PFC fibers to enter the ALIC and then follow the position of these fibers as they course through the ALIC. Overall, there is a clear dorsal-ventral topography within the ALIC. That is, fibers from dorsal PFC areas travel ventral to those from more ventral regions. However, we also found two other rules to the dorsal-ventral position that fibers take within the capsule. The rostral-caudal and medial-lateral cortical region of origin also plays a role in the dorsal-ventral fiber position within the capsule. In this respect, the rule is opposite for the dorsal PFC (dPFC), compared to the ventral PFC (vPFC). For fibers originating in the dPFC, the more rostral the cortical region, the more ventrally fibers traveled. In contrast, for the vPFC, the opposite was true. The more rostral the origin of the fibers, the more dorsally the fibers traveled within the ALIC. The dorsal-ventral position was also dictated by the medial-lateral cortical origin. Again, the opposite rule applied for the dPFC vs. the vPFC. For the dPFC, the more lateral the cortical origin, the more ventrally fibers travel in the ALIC; fibers from more medial areas travel more dorsally. For the vPFC, the more lateral the cortical origin, the more dorsally fibers travel in the capsule; fibers from more medial areas travel more ventrally. It appears that the cortical position may modulate the medial-lateral position of fiber in the ALIC. However, this was difficult to clearly determine in our data. Our results demonstrate that each of the four DBS VC/VS electrode contact involves a different subset of cortico-thalamic and brain stem fibers. The most ventral two contacts likely capture OFC and vmPFC fibers. The third contact is likely affects dACC fibers. The most dorsal contact captures area 10 fibers.

Conclusions: Taken together, fibers originate in most rostral PFC regions will travel in the center of the capsule. Those originating from the dPFC will be positioned dorsal to those from the vPFC. Axons from more caudal cortical dPFC and vPFC regions will fan out dorsally and ventrally within the capsule respectively. Likewise, fibers from the most lateral cortical dPFC and vPFC regions will also travel in the center of the ALIC. More medial dPFC and vPFC areas will contribute to the fibers in more dorsal and ventral positions respectively. These rules allow predictions of the relative positions PFC fibers are likely to occupy in the ALIC. These results have important implications for interpreting the neuroimaging studies that demonstrate changes in specific regions of the ALIC white matter in disease and after stroke and for identifying the likely connections that are associated with those changes. In addition, exploring the PFC-IC directional rules help us understand the effectiveness of DBS and the likelihood that the given PFC functional region may be captured by different DBS contacts.

Keywords: Prefrontal cortex, white matter, depression

Disclosures: Z. Safadi, Nothing to Disclose; S. Haber, Nothing to Disclose.

M232. Exploring Side Effects Similarity as a Novel Approach for Inferring Shared Mechanisms and Targets among Antidepressant and Anti-Inflammatory Drugs

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Background: It has been suggested that similarity in drug side effect profiles reflects a similarity in drug targets or

pathways (*Science* (2008); 321(5886): 263–266). As such, this provides a new dimension to explore in the context of identifying new indications for drug targets and pathways. The crosstalk between the immune system and depression has become an increasingly important area of interest. Multiple studies have shown that subsets of patients with major depressive disorder (MDD) have elevated levels of inflammatory cytokines such as CRP, TNF-α and IL-6. Further, prolonged treatment with cytokines such as IFN-α has been reported to induce depressive symptoms. While drugs targeting the immune system have been proposed to have an effect on mood, a large-scale empirical study of mechanistic similarity between anti-inflammatory and anti-depressant drugs based on clinical read-outs has not been published. Here we explore the space of approved drugs by comparing the drug side effect profiles of known anti-depressants and drugs targeting the immune system.

Methods: We measured the side effect similarities between 996 drugs in the Sider2 database based on drug label and between 1730 drugs in the FDA adverse event reporting system (AERS) database capturing postmarketing information. Weighted cosine similarity was calculated for each drug pair based on their side effect profiles in Sider2 with uncommon side effects weighted higher than more common ones. For drug-drug similarities based on AERS database, we used the cosine similarity matrix published by Takarabe *et al* (*Bioinformatics* (2012); 28(18): i611-i618). Clustering and drug-drug similarity networks generated based on the angular distance calculated from cosine similarity matrix were then analyzed to identify the close neighbors of antidepressants.

Results: Clustering of drugs revealed that the tricyclic antidepressants (TCA) formed a cluster distinct from other classes of antidepressants such as selective serotonin reuptake inhibitors (SSRI). Tramadol and Pregabalin, two non-antidepressants reported to be helpful in relieving depressive symptoms, were clustered together with SSRIs based on their side effect profiles. Further exploration of the side effect similarity network revealed multiple Cox inhibitors as close neighbors of SSRIs. One of the Cox-2 inhibitors, Celecoxib, has shown positive results in treating depression in multiple studies. Other Cox inhibitors with similar side effect profiles to antidepressants may be worth further study to test their potential as antidepressants. Another group of anti-inflammatory drugs showing high side effect similarity to antidepressants were glucocorticoids, supporting the idea that the glucocorticoid receptor may play a critical role in depression and antidepressant treatment. Also sharing high side effect similarities with antidepressants were interferon and Montelukast, a leukotriene antagonist, which are known to induce depression in some patients. The number of drugs targeting TNF-α and interleukins were very limited in the side effect databases. However, antidepressants Duloxetine and Pramipexolewere seen as close neighbors to TNF-α inhibitors Certolizumab and Lenalidomide in the side effect similarity network, respectively.

Conclusions: Our results indicate putative target/pathway-sharing between antidepressants and some anti-inflammatory drugs and support the idea that certain anti-inflammatory drugs may be helpful in relieving depressive symptoms. Side effect profile-based drug-drug similarity is particularly informative, since the side effect profile is a clinically meaningful measurement that results directly from a drug intervention in humans. However, it is only one of the many potential factors to use in computing drug similarity. Furthermore, certain drug structure specific side effects may be not directly relevant to interactions between a drug and its targets and thus can introduce noise to the analysis. Therefore, to further clarify the mechanistic similarities between antidepressants and drugs targeting the immune response system, analysis of additional drug similarity metrics based on drug structure, treatment-elicited gene expression signatures, pathway enrichment, and protein-protein interaction networks are ongoing.

Keywords: anti-depressant, inflammation, side-effects
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M233. Functional Network Connectivity Dynamics in Schizophrenia and Bipolar Disorder

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Background: Resting state Functional Magnetic Resonance Imaging (rsfMRI) studies can identify important characteristics of brain dysfunction in psychosis. Recent studies have acknowledged the nonstationarity of temporal dynamics of brain connectivity in resting state, thus emphasizing on the importance of understanding network dynamics to distinguish brain's different states. In this work, we compare the dynamicsof resting state fluctuations in healthy controls (HC), and age-matched samples of patients with schizophrenia (SZ) and bipolar disorder (BP). We use group independent component analysis framework (GICA) to examine the temporal dependence of the whole-brain functional network connectivity (FNC), defined as pairwise correlation between timecourses of intrinsic connectivity networks (ICNs), within these groups by exploiting the variability in brain connectivity. Instead of performing static FNC, we have implemented a very recent method to explore the dynamic FNC of different groups using a sliding- window approach.

Methods: In this study we used resting-state fMRI data from 159 subjects, which include 61 HC, 60 SZ and 38 BP subjects matched for age. Two hundred and ten volumes of data were acquired while the subjects were lying down with eyes open on a 3 T Siemens scanner with a repetition time of 2 sec. After initial standard preprocessing, the imaging data was decomposed into functionally homogeneous cortical and subcortical regions exhibiting temporally coherent connectivity using a high model order (100) group-level spatial independent component analysis (ICA). Out of the 100 components obtained, we selected 49 components as ICNs which depicted peak cluster locations in gray matter

with minimal overlap with white matter, ventricles and edges of the brain and also exhibit higher low frequency temporal connectivity. Subject specific time courses and spatial maps were obtained using back reconstruction approach as implemented in GIFT software. Instead of assuming stationarity in network connectivity between ICNs during the whole scan duration, we computed correlations between ICN timecourses using a sliding temporal window (Tukey window having a width of 22 TRs = 44 s; sliding in steps of 1 TR) to capture the variability in connectivity . From all of the dynamic windowed FNC matrices, we selected windows of higher variability as subject exemplars and used K-means clustering method to obtain group centrotypes. We determined the number of clusters to be 5 using the elbow criterion of the cluster validity index, which is computed as the ratio between within-cluster distances to between-cluster distance. These centrotypes are then used as starting points to cluster all of the dynamic FNC data. Group specific centrotypes were computed. Subject specific centrotypes were used to perform independent sample *t*-tests to probe for group differences.

Results: The identified 49 ICNs were categorized into seven sub-networks: subcortical, auditory, visual, sensorimotor, cognitive control, default-mode and cerebellar networks. The average connectivity matrix demonstrates a strong positive connectivity within subcortical, visual, sensorimotor, default-mode and cerebellar networks. A set of cognitive control (CC) regions also shows this positive connectivity among the regions, which are also connected to certain visual networks. These CC and visual regions show anti correlation to default-mode regions. Two sample t-tests did not reveal any group differences in static or overall connectivity. *K*-means clustering of dynamic FNC states revealed similar centroid of FNC states for HC, SZ and BP subjects for several cluster sizes searched ($K = 2$ to 9). Dynamic FNC analyses suggest that patients make fewer transitions to some states compared to healthy controls. Also initial results exhibit significant differences between groups in some dynamic FNC states between HC and BP subjects as well as HC and SZ subjects. HC showed greater connectivity than BP between one of the visual components and a thalamic component in one of the dynamic states (state 1). Also in another dynamic state (state 5), the same visual area was more strongly connected to a midline frontal component in HC than in BP. The differences were more pronounced between HC and SZ in a state (state 5) showing a pattern of both hypo and hyperconnectivity in the SZ group. Noteworthy to be mentioned that these significant differences cannot be identified using the conventional static functional connectivity analysis.

Conclusions: The whole-brain FNC dynamics can be well estimated using the sliding-window approach. By clustering the windowed FNC matrices, we are able to identify different patterns of FNC that are not recognized using the static FNC method. This study gives results, which may help us differentiate between different patient groups. Further study of FNC dynamics in both resting-state and task-related data for different groups will provide more robust estimation of the whole-brain connectivity, which will provide an important tool to better understand the brain changes associated with mental illness.

Keywords: schizophrenia; bipolar; resting state; functional network connectivity; fmri;

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M234. Dopamine DREADDs: Chemicogenetic Control of VTA Dopamine Activity During Reinstatement of Cocaine Seeking

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Background: Ventral Tegmental Area (VTA) is a crucial brain substrate of motivated behavior, but the specific neurons that are involved in these processes are poorly understood. While VTA dopamine neurons are clearly involved in reward, a lack of specific tools to selectively manipulate dopamine neurons has previously limited our ability to test their specific functions in behaving animals.

Methods: 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 pharmacologically inert in the absence of DREADDs). DREADD-expressing neurons can therefore be experimentally controlled in a highly selective, 'lock-and-key' manner via modulation of endogenous G protein signaling pathways. DREADDs can be targeted to VTA dopamine neurons via local microinjections of viral vectors containing a floxed DREADD gene into transgenic rats, whose dopamine neurons express Cre recombinase (TH::Cre rats). This approach allows 'remote control' of dopamine neuron activity via systemic injections of CNO. Here, we use viral vectors to express excitatory or inhibitory DREADDs (Gs, Gq, and Gi-coupled) bilaterally in VTA dopamine neurons of TH::Cre transgenic rats. We examined effects of inhibiting or exciting these dopamine neurons on cue-induced, cocaine-primed, and pharmacological stress (yohimbine)-induced reinstatement of cocaine seeking, as well as behavioral economic measures of cocaine motivation and value. We also examined effects of contralaterally disconnecting VTA dopamine neurons from their dense, reinstatement-related ventral pallidum (VP) afferents on cocaine seeking behavior.

Results: DREADD-based stimulation or inhibition of VTA dopamine neurons differentially modulated cocaine seeking in all three types of reinstatement. In addition, contralateral disconnection of VTA dopamine neurons from VP robustly attenuated cue-induced and cocaine-primed reinstatement, suggesting that VP connectivity with VTA dopamine populations is a crucial pathway mediating cocaine seeking.

Conclusions: These results show that stimulation of different G protein-coupled signaling pathways in VTA dopamine neurons results in distinct effects on drug seeking. We also show that communication between VTA dopamine neurons and their VP afferents is required for reinstatement of cocaine seeking. These findings show that VTA dopamine-containing neurons are crucially involved in wider circuits that mediate reinstatement of cocaine seeking in rats, and therefore are potentially involved in relapse to drug use in human addicts.

Keywords: DREADDs, reinstatement, dopamine, VTA, addiction

Disclosures: S. Mahler, Nothing to Disclose; B. Cox, Nothing to Disclose; G. Aston-Jones, Nothing to Disclose.

M235. Treatment of Dopaminergic Dysfunction in Schizophrenia Using Non-dopaminergic Mechanisms: A Computational Modeling Approach

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Background: A large body of research literature indicates that dopamine (DA) is involved in the genesis of schizophrenic symptoms, but the exact mechanism by which it exerts its effects remains unclear. Much current thinking suggests that schizophrenia may be associated with subcortical hyperdopaminergia and prefrontal cortex hypodopaminergia. Moreover, it has been suggested that while hyperdopaminergia—as posited by the original 'dopamine hypothesis'—may not be the sole cause of the illness, it may be involved in the exacerbation of symptoms, or at least some subset of them. Consistent with this is the fact that all currently used antipsychotics have some DA blocking activity. However, these agents are not universally effective for all schizophrenic patients at all times, and many carry highly debilitating side effect burdens. Here we present a drug identification process that is unique in that it centers on the system level dysfunction caused by hyperdopaminergia, and identifies novel agents that can re-equilibrate the system without acting through dopaminergic mechanisms. This *in silico* approach is made possible by the availability of computing platforms with processing capacity orders of magnitude greater than that of a generation ago, as well as information produced by the recent explosion in basic neuroscience research.
Methods: The computational model used in this study was based on our previously published simulation of hippocampus, and was implemented on our lab's 72 processor supercomputer. We included DA effects under that assumption that it is best regarded not simply as 'excitatory' or 'inhibitory'–rather, recent research has suggested that DA may alter the processing of information in a region specific manner. We applied the effects of DA by simulating its actions at the ion channel and synaptic level, in a concentration dependent manner, based on an extensive review of the neurophysiologic literature. DA was applied separately to (a) a control (unaffected) model, and (b) a schizophrenic model–that is, one which included NMDA hypofunction as well as decreased connectivity, implemented as decreased dendritic spine density. As a marker of the schizophrenic phenotype, we used a specific deficit in gamma band (40 Hz) oscillatory activity, a characteristic that has been shown repeatedly in the experimental literature. In trials using 20 'simulated patients' we found that DA had opposite effects on these two computational models: in the schizophrenic model, increasing DA led to a specific decrease in gamma band activity, but in the control model it modestly increased it. To the model (b) above (that is, the schizophrenic model with DA), we applied the effects of 2,000 simulated drugs. Specifically, we performed runs in which, separately and in combination, we: (a) decreased the decay time constant (T_2) of a particular GABA receptor subtype (α_2), in four gradations ; (b) increased GABA activity (conductance) in a generalized manner, in four gradations; (c) decreased the decay time constant (T_2) of the AMPA synapse, in five gradations; (d) increased calretinin cell projection strength, in five gradations; and (e) and increased NMDA conductance, in five gradations.
Results: A 'wellness metric' was established that indicated how closely a treated schizophrenic model approximated the control state. Applying this, we identified 49 virtual agents that may potentially be efficacious. Significantly, reducing $\alpha_2\hat{o}_2$ ((a) above) had ameliorative effects. Of particular interest, this showed marked interactions with other effects: a simulated medication with combined decreased α_2T_2 and decreased AMPA T_2 ((c) above) effects showed a robust and highly significant anti-schizophrenic effect, but an $\alpha_2\hat{o}_2$ decreasing + NMDA enhancing drug showed a weak effect. Two other joint effects that showed highly significant effectiveness were: (i) increased generalized GABA conductance ((b) above) + AMPA T_2 decrease, and (ii) AMPA $\hat{o}_2$ decrease + increased CR projection strength ((d) above). An ANOVA of these top 49 virtual medication runs revealed other statistically significant effects as well. To our knowledge, the combinations of effects detailed above have not previously been proposed for antipsychotic medications.
Conclusions: This work is significant for a number of reasons. First, it sheds light on the interactions between a number of putative neurobiological etiologies of schizophrenia—it suggests that DA's effects may vary based on the neural substrate on which it acts. Second, this work exhibits a process by which it is possible to perform pharmacologically relevant *in silico* experiments. Of course it is not entirely certain, clinically, what the analog of the high-DA state is. However, the findings outlined above have clear potential relevance, as medications that have the specific combinations of effects described may represent novel pharmacologic treatments for schizophrenia. These may be especially efficacious in certain phases of the illness (e.g., acute exacerbations), or in particular subgroups—and may act with a significantly lower side effect burden. More broadly, this research presents the possibility of a drug development approach in which the 'target' is not a receptor or a single neural entity, but rather a system level neurophysiologic behavior associated with schizophrenia.
Keywords: computational modeling hippocampus dopamine gamma oscillations drug discovery
Disclosures: P. Siekmeier, Nothing to Disclose; D. vanMaanen, Nothing to Disclose.

M236. Retinoid-related Orphan Receptor Alpha: A Novel Candidate Gene for Psychiatric Disease

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Background: Several recent association studies have identified the retinoid-related orphan receptor alpha (RORα) gene as a significant risk locus for post-traumatic stress disorder, bipolar disorder, and autism. Indeed, the naturally occurring *staggerer* RORα mutant and genetically engineered RORα

null mice demonstrate brain changes including: cerebellar atrophy, Purkinje cell atrophy and loss, degeneration of granule cells, and limted data showing structural changes in the olfactory bulb, in association with severe ataxia and other cerebellar dysunction. This restricted pattern of changes to the cerebellum in the RORa mutant leaves major gaps in any model trying to explain RORa gene-related susceptibility to this diversity of psychiatric disease. Therefore, in order to bridge this translation gap we conducted an investigation of the neuropsychological and neuroimaging intermediate phenotypes in a multiply affected family with a non-functional duplication of the RORa gene, and in RORa-deficient mice models.

Methods: Clinical, neuropsychological and genetic data were collected from six members of a single pedigree with three members harboring a rare duplication of isoform 1 of the RORα gene, presumably resulting in a frameshift leading to an early stop-codon and thus a non-functional protein. In addition, magnetic resonance imaging (MRI) was conducted on these same subjects, and fluorodeoxyglucose-positron emission tomography (FDG-PET) brain scans to quantify regional glucose metabolism were obtained from all family members and from 14 unrelated, normal age-matched controls (NC). FDG-PET data processing was carried out via voxel-based, canonical variates analysis and Scaled Subprofile Model of Principal Components analysis.

In a parallel experiment, laboratory generated homozygous (KO) ($N=13$) and heterozygous (HT) ($N=12$) RORα-deficient mice were compared to wild type (WT) ($N=11$) mice on performance on tests modeling cognitive deficits including novel object recognition and T-maze testing, and tests of locomotor activity and coordination including open field and rotarod tests. In addition, brain glucoe metabolism (BGluM) was assessed in these mice using [18F] FDG micro-PET.

Results: The three family members harboring the RORα duplication carried diagnoses of schizophrenia, schizoaffective disorder and major depression. Moreover, the three affected family members demonstrated significant neuropsychological dysfunction, whereas none of the three family members without the RORα duplication demonstrated any neuropsychological impairments. T1-weighted MRI images demonstrated all three individuals harboring the duplication to have peri-sylvian fissure and pre-pontine atrophy in addition to ventricular enlargement. None of the three family members without the duplication showed any anatomical abnormalities on MRI. FDG-PET data robustly differentiated the three family members with the RORα duplication from the family members without the RORα duplication and all NC subjects ($p<0.05$). A unique pattern of white matter (WM) hyper-metabolism observed in the corpus callosum, internal capsule, in the vicinity of the medial prefrontal cortex, temporal cortex, and sensorimortor cortex and hypo-metabolism observed in the vicinity of the sensorimotor cortex, occipital cortex, and inferior parietal cortex was unique to the three family members affected with the RORα duplication compared to family members without the RORα duplication and all NC subjects. Neuropsychological test performance of the mice demonstrated KO mice had a significantly decreased ability to recognize novel objects compared to both WT and HT mice. Moreover, KO mice had a significantly lower percentage of correct trials on the T-maze compared to both WT and HT mice. Micro-PET data demonstrated significant hypo-activation in KO animals compared to WT animals in the rhinal cortex, cerebellum, paraflocculuc, thalamic nucleus, primary somatosensory cortex, lateral orbital tract, and piriform cortex. Contrastingly, KO animals showed significant hyper-activation compared to WT animals in the periaqueductal gray, colliculi, olfactory bulb, cerebellar nuclei, and striatum. Moreover, KO mice showed a significant negative correlation between activation at both the cerebellum ($r=-0.839$, $p<0.05$) and the periaqueductal gray ($r=-0.829$, $p<0.05$) and the percentage of correct trials during T Maze testing.

Conclusions: These data provide the first evidence that disruption of the RORα gene has negative structural and functional brain consequences outside the cerebellum. Indeed, the unique patterns of both abnormal hypo- and hyper-activation associated with RORα disruptions in the human and animal subjects, and its correlation with impaired spatial memory, suggests abnormalities in the synchrony of interconnected neural networks possibly contributing to the susceptibility to a diverse array of psychiatric disease. Further investigation is warranted.

Keywords: Retinoid-related orphan receptor alpha, cerebellum, MRI, PET, human, mice

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M237. Early Adverse Life Events: Interactions with Corticotropin Releasing Hormone Receptor 1 and Progestoerone Receptor Polymorphisms Healthy Controls and Patients with Chronic Abdominal Pain

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Background: Although genetic and environmental influences interact to contribute substantially to vulnerability for illness, the search for direct genetic x environmental influences contributing to the risk for Irritable Bowel Syndrome (IBS) have been inconclusive so far. Genes regulating the effects of stress via the HPA axis have been implicated in the physiological and pathological regulation of stress reactivity as mediated by the release of hypothalamic corticotrophin releasing hormone (CRH). HPA activity is modulated by sex hormones progesterone and estrogen. HPA axis hyperactivity may be a function of psychosocial environmental stressors such as early adverse life events (EALs) and may show sex-specific effects on emotional arousal circuitry in the brain. The hippocampus is a major component of the emotional arousal system whose morphology and gene expression is modified by early life trauma.

Aims: To examine gene-environment interactions influencing hippocampal volumes in male and female IBS patients and HCs. CRH-R1, CRHBP, NR3C1, FKBP5, PGR, and ESR1 polymorphisms were examined for effects on hippocampal volumes and interactions with early life trauma, sex, and diagnosis.

Methods: In a racially diverse community population of IBS and HCs, three SNPs of the CRH-R1 gene (rs7209436, rs110402, and rs242924), 2 SNPs of the CRHBP gene (rs10055255 and rs 10062367), 3 SNPs of the NR3C1 gene (rs33389, rs2963155, rs41423247), 3 SNPs of the FKBP5 gene (3800373, rs9296158, rs1360780), 2 SNPs of the PGR gene (rs104f2838, rs10895068) and 1 SNP of the ESR1 gene (rs9340799) were genotyped. Subjects completed structural MRI scans and the volumes of the right and left hippocampus were computed. Superloci were created using Mendel software for each gene of interest and were analyzed in a linear regression model controlling for age, race, and total brain volume. We tested for main effects of genotype, sex, diagnosis, early life trauma index (ETI) as well as interactions between genotype and ETI with sex and diagnosis.
Results: 122 IBS patients (91 female) and 205 HCs (female 164) were studied. Significant Sex x Gene x ETI interactions were seen for PGR and CRH-R1 superloci with the right hippocampus and for PGR with the left hippocampus. For males with PGR minor alleles, higher ETI was associated with smaller right and left hippocampal volumes, while no effect was seen in females. For males with CRH-R1 major alleles, higher ETI was associated with smaller right hippocampal volume.
Conclusions: Sex differences in interactions between EALs and polymorphisms in genes directly involved or modulating the stress reactivity CRH system were demonstrated for volume of the hippocampus, a region involved in emotional arousal. Specifically, PGR and CRH-R1 demonstrated male-specific effects of ETI on hippocampal volume. Both PGR and CRH-R1 are expressed in the hippocampus. Progesterone is involved in neurogenesis and modulates HPA activity. The results highlight the importance of considering sex in examining gene-environment effects in IBS.
Keywords: early adverse life events, hippocampus, brain volume, progesterone, hypothalamic corticotrophin releasing hormone, irritable bowen syndrome.
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M238. Vocational Outcome in Patients with Psychotic and Affective Disorders: A Nation-wide, Historical-prospective Study

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Background: The large waves of deinstitutionalization of the seventies and eighties were supposed to be followed by reintegration of the previous mentally ill patients into society, including into the working force. Effective pharmacological treatments were expected to facilitate this process and vocational training programs were expected to provide the necessary skills. While deinstitutionalization was overall successful, reintegration into the working force continues to be a challenge. Several relatively small studies using various measurements investigated the outcome of specific vocational interventions but no nation-wide survey of gainful employment of patients with severe mental disorders has ever been reported. We assessed the employment status of 19 959 patients with schizophrenia 11 374 patients with other non-affective psychosis and 4340 patients with bipolar disorder.
Methods: Data from the Israeli Psychiatric Hospitalization Case Registry were linked with data from the National Insurance Institute (the equivalent of the US Social Security) which contains nation-wide data on personal income. Mean follow-up starting with the first admission was 11.2 ± 5.3 years, range: 2–21 years. Among these patients, 9726 had only one admission for either schizophrenia ($n = 4449$) or other non-affective psychotic disorder ($n = 5277$), and 21 607 had repeated admissions (mean number of admissions was 6.3 ± 6.4) with any non-affective psychotic disorder. 1561 bipolar disorder patients had a single admission, and 2779 had 4.5 ± 4.1 admissions. Gainful employment was considered an average of at least 1000 USD per month which was the approximate minimal wage at the time of the survey.
Results: The percentages of patients earning minimum wage or above were: patients with one admission and schizophrenia 7.2%, non-affective psychotic disorders 18.9 and 20.5% patients with bipolar disorders; 3.6% of patients with multiple admissions and schizophrenia or non-affective psychosis and 13.1% with bipolar disorder. At the time of the survey approximately 50% of the Israeli general population were employed and the rate of unemployment was 6.8%.
Conclusions: Patients admitted for schizophreniaor bipolar disorders have a poor employment outcome, even if they are admitted only once. These results indicate that currently available pharmacological and vocational interventions might not be appropriate and sufficient to re-integrate these individuals into the working force and that different and more resources should be devoted towards this end.
Keywords: vocational intervention, psychotic disorders, affective disorders.
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