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W1. Validation of a Procedurally Simple Murine Model of Methamphetamine Addiction Vulnerability/ Resiliency in Mice

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Background: Individual variation exists with respect to the development and severity of drug addiction and this individual variability reflects a combination of environmental and genetic factors. However, the biochemical correlates of addiction vulnerability/resiliency are severely understudied, particularly to the highly addictive psychomotor stimulant methamphetamine (MA). Even in presumably genetically homogeneous populations of C57BL/6J (B6) mice, marked variability exists with respect to the capacity of repeated MA (4X2 mg/kg) to elicit place-conditioning, an index of MA's motivational/affective valence. While approximately 50% of B6 mice exhibit a conditioned-preference (CPP) for a MA-paired environment, approximately 12% show conditioned aversion (CPA), and the remaining mice exhibit ambivalence or no conditioned response (Neutral).
Methods: We tested the predictive validity of studying inbred B6 mice under simple place-conditioning procedures as a high-throughput strategy for the study of MA addiction vulnerability/resiliency, by correlating phenotype with MA-induced locomotor activity, by assaying CPP-, Neutral- and CPA-B6 mice in a place-conditioning version of the extinction/reinstatement paradigm, as well as an oral MA self-administration paradigm (10-40 mg/L). We also tested the construct validity of this model by examining for phenotypic differences in the expression of glutamate-related proteins within the nucleus accumbens core.
Results: CPP Score was inversely correlated with acute MA-induced locomotor hyperactivity, but positively correlated with the extent to which mice developed locomotor sensitization during MA-conditioning. The MA-conditioned response was more resistant to extinction in CPP-B6 mice vs. CPA counterparts and a 2 mg/kg MA challenge injection reinstated the conditioned response following extinction only in CPP-B6 mice. CPP-B6 mice also exhibited greater MA-directed responding during the first several days of self-administration when 20 mg/L MA served as the reinforcer, but did not differ from Neutral or CPA mice regarding MA intake of this dose at any time during study. When the dose-response function for MA intake was examined, CPP-B6 mice consumed higher amounts of the 10 mg/L and 40 mg/L solutions, and their CPP Score predicted the intake of the 10 mg/L dose. A comparison of response elasticity in response to 10 mg/L MA under increasing schedules of reinforcement (FR1-FR40), indicated higher intake of this dose under low reinforcement schedules by CPP-B6 mice, and intake was predicted under both FR1 and F2 reinforcement schedules by CPP Score. However, there were no group differences in elasticity. Immunoblotting revealed higher Homer2 expression, which is consistent with prior results from MA-sensitized B6 mice and mice selectively bred for high MA intake and might underpin the addiction vulnerable phenotype of CPP-B6 mice.
Conclusions: Together, these results provide predictive and construct validity for our B6 place-conditioning model as a high-throughput tool for studying the biobehavioral mechanisms of MA addiction vulnerability/resilience of to our understanding of the etiology and treatment of MA addiction.
Keywords: resiliency, addiction, vulnerability, homer.
Disclosure: Nothing to Disclose.

W2. Robust, Scalable, and Cost-effective High Throughput Production of iPSC-derived Neural Stem Cells/Early Neural Progenitor Cells and Their Differentiation into Glutamatergic Neurons

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Background: Induced pluripotent stem cell (iPSC)-based technologies have revolutionized research into human diseases by enabling the generation of specified cells in a renewable manner from individuals of interest. Human iPSC-based models also offer an unprecedented opportunity to perform high throughput screens of novel drugs for neurological and neurodegenerative diseases. Such screens require a robust and scalable method to generate large numbers of uniformly distributed, differentiated mature neuronal cells. Currently, available methods based on differentiation of embryoid bodies (EBs) or directed differentiation of adherent culture systems are either expensive or are not scalable.
Methods: We developed a protocol that enabled high throughput generation of neuronal stem cells (NSCs)/early neural progenitor cells (eNPCs) from iPSCs. These cells were stored or transferred into 384 well plates and differentiated into neurons. At least twenty-four 384-well plates at a density of 3.5 x103 NSCs/NPCs/well could be generated from a confluent 6-well plate of iPSCs in 4 weeks at a cost of $ 28/plate.
Results: Following culture in neurobasal medium supplemented with B27 and BDNF, NSCs/eNPCs principally differentiated into glutamatergic neurons expressing markers characteristic of forebrain layer 3 pyramidal cells. Whole-cell patch-clamp experiments indicated that most

iPSC-derived neurons express functional ligand-gated channels.
Conclusions: The procedure detailed here enables robust, scalable, and cost-effective generation of neurons in numbers required for high-throughput screening.
Keywords: Induced pluripotent stem cells (iPSCs), Neuronal stem cells (NSCs), High throughput screening, In vitro neuronal differentiation.
Disclosure: Nothing to Disclose.

W3. Brexpiprazole for the Treatment of Acute Schizophrenia: A Randomized, Controlled Trial

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Background: To evaluate the efficacy, and safety/tolerability of brexpiprazole in patients with acute schizophrenia.
Methods: This was a phase III, multicenter, randomized, double-blind, placebo-controlled trial (NCT01396421). Patients with acute schizophrenia were randomized to fixed doses of brexpiprazole 4 mg, 2 mg, 0.25 mg, or placebo (2:2:1:2) for 6 weeks. The primary efficacy endpoint was change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to week 6; key secondary endpoint was the change in Clinical Global Impression-Severity Scale (CGI-S) score at week 6. Efficacy analyses were conducted using mixed model repeated measures (MMRM), including treatment, visit, site and treatment-by-visit interaction as fixed effects, and baseline score-by-visit as covariate. A gate keeping average effect method was applied to control for multiple comparisons (at an alpha level of 0.05) before proceeding with the comparisons for 2 mg and 4 mg brexpiprazole versus placebo. The 0.25 mg group was included to establish a non-effective or minimally effective dose range of brexpiprazole.
Results: The gate keeper test of the average effect method met the threshold for the combined dose of brexpiprazole 4 mg/day and 2 mg versus placebo ($p < 0.0001$). Brexpiprazole 4 mg ($n = 178$) and 2 mg ($n = 180$) were each superior to placebo ($n = 178$) in change from baseline in PANSS total score at week 6 (least square mean change: -19.65 vs -12.01, $p = 0.0006$ and -20.73 vs -12.01, $p = < 0.0001$, respectively). Brexpiprazole 0.25 mg ($n = 87$) showed minimal improvement over placebo at week 6 ($p = 0.2910$). Results of the key secondary endpoint and other secondary endpoints supported the primary results. Most frequent adverse events in the brexpiprazole groups (incidence > 5% in any group and more than twice the incidence in the placebo group) were diarrhea (3.9%, 1.6%, 5.6%, 1.6%) and akathisia (7.2%, 4.4%, 0.0%, 2.2%), in the brexpiprazole 4 mg, 2 mg, 0.25 mg, and placebo groups, respectively.
Conclusions: Brexpiprazole 4 mg and 2 mg were effective in treating adults with acute schizophrenia, and superior to placebo in the primary and key secondary efficacy endpoint, measured by the change in PANSS total score and CGI-S, respectively. All doses of brexpiprazole were well tolerated.
Keywords: Schizophrenia, Phase III trial, Brexpiprazole, Efficacy and safety.
Disclosure: I (Christoph Correll) have been a consultant and/or advisor to or have received honoraria from: Actelion, Alexza; American Academy of Child and Adolescent Psychiatry, Bristol-Myers Squibb (BMS), Cephalon, Eli Lilly, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Lundbeck, Medavante, Medscape, Merck, Janssen/J&J, Otsuka, Pfizer, ProPhase, Roche, Sunovion, Takeda, Teva and Vanda. Income sources and equity of $10,000/year or greater: BMS, Janssen/J&J, Lundbeck, Otsuka, Pfizer, ProPhase. Financial involvement with a company constituting > 5% of personal income: BMS, Lundbeck, Otsuka, Pfizer, ProPhase. Funding received from: BMS, Feinstein Institute for Medical Research, Janssen/J&J, National Institute of Mental Health, National Alliance for Research in Schizophrenia and Depression and Otsuka. Drs. Skuban, Youakim, Ouyang, Hobart, Pfister, McQuade, Nyilas, Carson and Sanchez are employees of Otsuka Pharmaceutical Commercialization and Development, Inc. Funding for this study was provided by Otsuka Pharmaceutical Commercialization and Development, Inc. (Princeton, USA) and H. Lundbeck A/S (Valby, Denmark).

W4. A Pooled Analysis of 3 Randomized, Placebo-Controlled, Phase 3 Studies Evaluating the Efficacy, Safety, and Tolerability of Adjunctive Armodafinil in Bipolar I Depression

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Background: Depressive episodes associated with bipolar I disorder may warrant adjunctive pharmacotherapy. Indeed, lurasidone is FDA-approved as adjunct therapy with lithium or valproate for bipolar I depression. Armodafinil (R-modafinil) is a wakefulness-promoting, low-affinity dopamine transport inhibitor currently approved in the US for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work disorder. Earlier research on modafinil and armodafinil provided a signal for potential benefit as adjunctive treatment for acute bipolar depression. Subsequently, 3 similarly designed phase 3 studies investigating adjunctive armodafinil in bipolar depression yielded varying efficacy results (only 1 with statistical significance vs placebo; 2 with a non-significant numerical advantage vs placebo). Here we present a pooled analysis of these 3 phase 3 studies.
Methods: Pooled analysis of 3 multicenter, randomized, double-blind, placebo-controlled studies investigating the addition of armodafinil 150 or 200 mg/d (200 mg/d dose in 2 studies only) in adults aged 18-65 years with bipolar I depression despite taking protocol-defined "mood stabilizers" (lithium, valproate, lamotrigine, olanzapine, risperidone, aripiprazole, ziprasidone [ziprasidone only in combination with lithium or valproate in 2 studies; only in combination with lithium, valproate, or lamotrigine in 1 study], or quetiapine [1 study only]). The primary efficacy assessment was mean change from baseline to week 8 in the

30-item Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C30) total score analyzed by mixed-model repeated measures. Secondary efficacy assessments included mean change from baseline in IDS-C30, IDS-C30 response ($\geq$50% final reduction from baseline total score) rates, and IDS-C30 remission (final IDS-C30 $\leq$11) rates, each assessed at weeks 1, 2, 4, 6, 7, and 8 (or early termination). Randomization to 200 mg/d (2 studies) was discontinued early; only safety data are reported for this group. Safety/tolerability assessments included adverse events (AEs) and discontinuations due to AEs . Continuous variables were analyzed using analysis of variance, and categorical efficacy variables using the Cochran-Mantel-Haenszel test.

Results: Overall, 1,261 patients with bipolar I depression (mean age 44.0 years, 60% female, 82% white) were evaluable for efficacy (633 taking adjunctive armodafinil 150 mg/d and 628 taking adjunctive placebo). In total, 491 (78%) patients taking armodafinil 150 mg/d and 497 (79%) taking placebo completed the studies. Baseline mean IDS-C30 scores were 43.1 and 43.3 for the adjunctive armodafinil 150 mg/d and adjunctive placebo groups, respectively. For primary efficacy, least-squares mean ± standard error IDS-C30 change from baseline at week 8 was -21.2 ± 0.59 with adjunctive armodafinil 150 mg/d and -18.8 ± 0.59 with adjunctive placebo ($P = 0.0021$). Secondary efficacy parameters showed statistical significance for adjunctive armodafinil 150 mg/d over adjunctive placebo on the IDS-C30 change from baseline at weeks 6 ($P = 0.0476$), 7 ($P = 0.0020$), 8 ($P = 0.0016$), and end point ($P = 0.0138$); IDS-C30 response at weeks 7 ($P = 0.0029$), 8 ($P = 0.0026$), and end point ($P = 0.0165$); and IDS-C30 remission at week 8 ($P = 0.0345$) and end point ($P = 0.0361$). The safety population included 1,317 patients (691 taking adjunctive armodafinil 150 or 200 mg/d; 626 taking adjunctive placebo). Overall, 351 (51%) patients taking adjunctive armodafinil (150 or 200 mg/d) and 264 (42%) taking adjunctive placebo had $\geq$1 AE. Only 4 AEs occurred in $\geq$5% in either treatment group, including headache: 97 (14%) vs 65 (10%); nausea: 47 (7%) vs 21 (3%); diarrhea: 40 (6%) vs 28 (4%); and insomnia: 34 (5%) vs 20 (3%) in the adjunctive armodafinil 150 or 200 mg/d vs adjunctive placebo groups, respectively. AEs led to discontinuation in 41 (6%) patients taking armodafinil 150 or 200 mg/d and 29 (5%) taking adjunctive placebo.

Conclusions: While 3 phase 3 investigations of armodafinil as adjunctive treatment for bipolar I depression yielded varying efficacy results (only 1 with statistical significance vs placebo; 2 with a non-significant numerical advantage vs placebo), a pooled analysis of these 3 similarly designed studies demonstrated that adjunctive armodafinil 150 mg/d provided a statistically significant improvement in major depressive episode symptoms associated with bipolar I disorder as measured by the mean change in IDS-C30 at week 8 (primary efficacy parameter). This finding was further supported by several secondary efficacy outcomes. Adjunctive armodafinil was generally well tolerated across all 3 studies, with nearly equal percentages of patients discontinuing due to AEs with adjunctive armodafinil vs adjunctive placebo. This pooled analysis of 3 phase 3, randomized, double-blind, placebo-controlled trials suggests that armodafinil may have a favorable benefit-to-risk ratio in some patients with bipolar I depression; further studies are necessary for confirmation.

Keywords: Bipolar I Depression, Efficacy, Safety, Tolerability.

Disclosure: J. Amchin and R. Yang are employees of Teva Pharmaceuticals. T. Ketter and M. Frye are consultants for Teva Pharmaceuticals. This study was sponsored by Teva Pharmaceuticals. Medical writing support was provided by John H. Simmons, MD, at Peloton Advantage, LLC, and was funded by Teva Pharmaceuticals.

W5. Validation of A Computerized Assessment of Functional Capacity

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Background: Assessment of functional capacity is critical to the treatment of cognitive impairments in schizophrenia. Current methods are highly correlated with performance on neuropsychological tests, but suffer from compromised ecological validity due to reliance on role playing exercises. Methods of assessment with improved ecological validity are acutely needed. In response, we have developed a computerized virtual reality assessment that contains the components of a shopping trip, including searching the pantry, making a list, taking the correct bus, shopping, paying for purchases, and getting home. Previous pilot studies indicated that the assessment of functional capacity with virtual reality methodology is feasible, and suggested such a tool may meet criteria for use as a co-primary measure. The primary aims of the current study were to extend our previous results to 1) assess the validity, sensitivity, and reliability of the Virtual Reality Functional Capacity Assessment Tool (VRFCAT) as a primary measure of functional capacity in schizophrenia; 2) examine the VRFCAT's ability to quantify changes in functional capacity by comparing it to the UCSD Performance-based Skills Assessment (UPSA-2-VIM); and 3) determine the association between performance on the VRFCAT and performance on the MATRICS Consensus Cognitive Battery (MCCB), which is the gold standard measure of cognition in pharmaceutical clinical trials regulated by the FDA.

Methods: Participants included 160 patients with schizophrenia (91 male, 69 female) and 158 healthy controls (80 Male, 78 Female). All subjects completed the VRFCAT, UPSA-2-VIM < and the MCCB at Visit 1. The VRFCAT and UPSA-2-VIM were completed again at Visit 2. Key outcome measures for the VRFCAT included total time to complete all objectives as well as errors. Analyses examined test reliability as well as performance differences and correlations between measures.

Results: High test-retest reliability was demonstrated for VRFCAT Total Completion Time in both Patient and Control groups (ICCs = 0.80 and 0.78 respectively). Test-retest reliability for the UPSA-2-VIM was also high for both groups (ICCs = 0.77 and 0.78 for Patients and Controls, respectively). VRFCAT Total Completion time was negatively correlated with both UPSA-2-VIM ($r = -0.55$, $p < 0.0001$ for patients and -0.65, $p < 0.0001$ for controls)

and MCCB Composite ($r = -0.50$, $p < 0.0001$ for patients and -0.64, $p < 0.0001$ for controls). A composite score will be developed once data collection has been finalized.
Conclusions: Findings extend previous results and indicate the VRFCAT is a highly reliable and sensitive measure of functional capacity with associations to the UPSA-2-VIM and MCCB. These results provide encouraging support for a computerized functional capacity assessment for use in schizophrenia.
Keywords: Functional capacity, Cognition, Schizophrenia, Aging.
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W6. Optimizing Treatment with Lurasidone in Patients with Schizophrenia: Results: of a Randomized, Double-blind, Placebo-controlled Trial (OPTIMIZE Trial)

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Background: Lurasidone, in the dose range of 40-160 mg/day, has demonstrated efficacy in the treatment of patients with acute schizophrenia, based on the results of 5 short-term, fixed-dose, placebo-controlled studies. Treatment with doses lower than 40 mg/d has not been evaluated in interpretable placebo-controlled trials where assay sensitivity has been established. The aims of the current study were to evaluate the efficacy of lurasidone 20 mg/d in patients with an acute exacerbation of schizophrenia; and to determine an optimal treatment strategy for patients not achieving a clinically meaningful reduction in the Positive and Negative Syndrome Scale (PANSS) total score by Week 2 of standard dose lurasidone treatment.
Methods: In this multiregional study, hospitalized patients, age 18-75 years, with an acute schizophrenic exacerbation were required to have a PANSS total score ≥ 80, a PANSS subscale score ≥ 4 (moderate) on ≥ 2 PANSS items (delusions, conceptual disorganization, hallucinations, unusual thought content), and a CGI-S score ≥ 4. Eligible patients were randomized to double-blind treatment with a fixed dose of lurasidone 20 mg/d (for 6 weeks), or lurasidone 80 mg/d (for 2 weeks), or placebo (for 6 weeks), in a 1:2:1 ratio. After two weeks of treatment, patients demonstrating early improvement ($\geq 20\%$ reduction in PANSS by Week 2) in the lurasidone 80 mg group were continued on the same dose for the remaining 4 weeks of the study. Patients with $< 20\%$ PANSS improvement were re-randomized, in a 1:1 ratio, to receive either lurasidone 80 mg/d, or lurasidone 160 mg/day for the remainder of the double-blind phase. The primary efficacy variable (change from baseline in PANSS total score) was assessed using a mixed model for repeated measures (MMRM) analysis. Change from baseline in the Clinical Global Impression, Severity (CGI-S) scale was the key secondary variable.
Results: The intent-to-treat population consisted of 101 patients randomized to lurasidone 20 mg/d (male, 64.4%; mean age, 41.5 years; baseline PANSS, 96.7), 198 patients on lurasidone 80 mg/d (male, 60.1%; mean age, 40.5 years; Baseline PANSS, 96.7), and 112 patients on placebo (male, 69.6%; mean age, 40.7 years; Baseline PANSS, 97.8). Lurasidone 20 mg/d did not demonstrate significant improvement vs. placebo at Week 6 (-17.6 vs -14.5; P = ns; primary efficacy endpoint). Change in the CGI-S score was also not significant for lurasidone vs placebo at week 6 (-0.93 vs -0.73; P = ns). Patients with early non-response (at Week 2) to standard dose treatment with lurasidone ($n = 43$) who were randomized to lurasidone 160 mg/d achieved significantly greater improvement in PANSS total score at Week 6 study endpoint compared with non-responding patients ($n = 52$) who continued on the 80 mg/d dose (-16.6 vs. -8.9; $p = 0.023$). Improvement in the CGI-S score was non-significantly greater for lurasidone 160 mg/d vs 80 mg/d at Week 6 (-1.0 vs -0.6; P = ns). Overall discontinuation rates during double-blind treatment were lower for lurasidone (combined doses, 27%) compared with placebo (38%); discontinuation due to adverse events was also lower for lurasidone (3%) compared with placebo (7%). There was no dose-related increase in discontinuation on lurasidone. Median change in weight was similar for lurasidone (combined doses) vs placebo ($+0.30$ kg vs $+0.10$ kg); no dose-related effect on weight was noted.
Conclusions: In this double-blind, randomized, 6-week trial in patients with acute schizophrenia, treatment with lurasidone 20 mg/d did not result in significant improvement compared with placebo. Patients randomized to lurasidone 80 mg/d who did not show clinically significant improvement by Week 2 achieved significantly greater improvement in PANSS total score at Week 6 after treatment with 160 mg/d compared with 80 mg/d. Early dose escalation was not associated with a reduction in tolerability. Clinicaltrials.gov Identifier: NCT01821378 Sponsored by Sunovion Pharmaceuticals Inc.
Keywords: Schizophrenia, Lurasidone, Antipsychotic agents.
Disclosure: Antony Loebel, Robert Silva, Robert Goldman, Kei Watabe, and Josephine Cucchiaro are employees of Sunovion Pharmaceuticals Inc. John Kane has received honoraria for lectures and/or consulting from Alkermes, Amgen, Bristol-Myers Squibb, Cephalon, Eisai, Boehringer Ingelheim, Eli Lilly, Forrest, Genentech, Intracellular Therapeutics, Janssen, Johnson and Johnson, Lundbeck,

Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Reviva, Roche, Sunovion and Targacept. He is a shareholder of MedAvante.

W7. Adolescents' Amygdala Response to Personally Relevant Social Reward: Functional Connectivity and Association with Depressive Symptoms

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Background: During adolescence, peer experience changes in nature: peer social rewards such as close friendships become more salient, and social goals focus on abstract peer outcomes (e.g., obtaining social status). Adolescence is also the vulnerable period for the onset of depression, a disorder of disrupted social functioning whose etiology is thought to involve disrupted neural reward circuitry in the context of challenges to social goals (Davey, Yücel, & Allen, 2010). The amygdala is a key component of the salience network, has been broadly implicated in depression, and responds to rewards and social stimuli. Using a newly developed, personally relevant peer social reward paradigm in a sample of typically developing adolescents, we examined functional connectivity of the amygdala and its relation to depressive symptoms.
Methods: Participants were 49 typically developing adolescents (41% Male; 72% European American) between the ages of 14 and 18 ($M = 16.36$) with no history of diagnosis or treatment of affective, developmental, or behavioral disorders. During a laboratory visit, participants were video recorded interacting with their best same-sex friend in a conversation about their most pleasant mutual experience. At a later functional magnetic resonance imaging assessment on a 3T Siemens TIM Trio scanner, participants viewed 30-s video clips of their friend or an unfamiliar peer displaying positive affect or neutral affect. Participants completed the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). Psychophysiological interaction with the bilateral amygdala as seed region was conducted in SPM8 to compute functional connectivity during friend positive affect compared with stranger positive affect. Family-wise error correction at $p < .05$ was applied to adjust for multiple comparisons. Conjunction analyses in SPM8 tested whether clusters resulting from PPI analyses were associated with depressive symptoms.
Results: Participants exhibited negative functional connectivity between the amygdala and regions implicated in the salience network and in reward processing: anterior cingulate cortex, insula, dorsolateral prefrontal cortex, and caudate (e.g., for DLPFC: 7741 voxels; [22, 20, 2]; $t = 4.62$). Higher level of depressive symptoms was associated with greater functional connectivity between the amygdala and the insula (left: 2194 voxels, [− 36, 18, − 8], $t = 4.11$; right: 2108 voxels, [14, 14, -12], $t = 3.69$) and between the amygdala and medial prefrontal cortex (3724 voxels; [32, 6, 64]; $t = 3.50$).
Conclusions: In typically developing adolescents, personally relevant social reward elicits a coordinated response in a set of regions associated with the salience network and with reward processing. Focusing on the amygdala as the seed region for this functional connectivity is consistent with prior research implicating the amygdala in the brain's salience network and the processing of social and rewarding stimuli. The association of functional connectivity during peer social reward with depressive severity suggests that depression could involve high sensitivity to social cues, with resulting differences in appraisal of peer positive affect. One possibility is that functional coordination of this set of regions, often implicated in negative affect, generalizes inappropriately to pleasant stimuli in depression. Understanding these mechanisms may be helpful in elucidating the pathophysiology and development of depression.
Keywords: depression, amygdala, adolescent, reward.
Disclosure: Nothing to Disclose.

W8. Interleukin 6 is a Mediator Between Maternal Prenatal Anxiety and Infant Development of Cerebral Inhibition

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Background: Prenatal exposure to maternal anxiety increases the risk for a variety of adverse behavioral and neurocognitive outcomes. However, there has been little consensus as to potential mediators of this relationship. Cytokines are altered by anxiety, yet cytokines have not been actively investigated as potential mediators.
Methods: Forty-five pregnant women were assessed, at 16 and 28 weeks gestation, for serum cytokines Il-1b, Il-6, interferon gamma, and TNF-alpha. Maternal anxiety was assessed with the State-Trait Anxiety Index (STAI). Cerebral inhibition was assessed in 1-month old offspring using P50 sensory gating.
Results: Replicating previous work, for full-term infants, elevated lifetime (trait) but not current (state) anxiety predicted elevated (impaired) infant P50 sensory gating (Spearman $p\ (43) = 0.29$, $p = .046$). 16 week maternal Il-6 levels were inversely correlated with both maternal trait anxiety (Spearman $p = -0.3966$, $p = .011$) and infant P50 sensory gating (Spearman $\rho\ (26) = -0.5373$, $df = 26$, $P = 0.0032$).
Conclusions: Maternal Il-6 may mediate the relationship between maternal anxiety and early development of cerebral inhibition. Prenatal choline supplementation, in healthy human pregnancies, improves early development of cerebral inhibition. Prenatal choline supplementation may be a way to ameliorate the effects of maternal anxiety.
Keywords: cytokine, sensory gating, P50, infant.
Disclosure: Nothing to Disclose.

W9. Brain Activity and Connectivity Underlying Hypnosis

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Background: Hypnosis has proven clinical utility, yet changes in brain activity underlying the hypnotic state

have not yet been identified. Hypnosis is a state of highly focused attention coupled with a reduction in distraction. Such a mental state enhances non-judgmental openness to input from others and can increase receptivity to therapeutic instruction. Clinically, hypnosis is used to reduce pain, anxiety, and phobias, improve symptoms of intestinal disease, and control nonepileptic seizures. Hypnotizability is a measurable trait which is more stable than IQ over a 25 year span. There is recent evidence of differences in resting state fMRI between individuals who are high and low in hypnotizability. Hoeft et al. found increased functional connectivity of the left anterior aspects of the DLPFC and the dACC nodes of the salience network (SN) in high hypnotizables compared with lows, while decreased default mode network (DMN) activity has also been reported in high hypnotizables compared with lows. The unresolved issue addressed in this study is the specific brain activity underlying the state of hypnosis itself.

Methods: We screened 545 participants for hypnotizability using the Harvard Group Scale for Hypnotic Susceptibility, Form A (Shor and Orne, 1962) the Hypnotic Induction Profile (Spiegel and Spiegel, 2004). 36 highs and 21 lows who scored consistently high or low on both measures, representing 10.5% of the sample screened, participated in the brain imaging studies. Subjects underwent four conditions in the MRI scanner administered in counter-balanced order: resting with eyes closed, autobiographical memory retrieval, and two hypnotic conditions, remembering or imagining a time when they felt happiness (hypnotic emotion condition), and a vacation (hypnotic memory condition).We used fractional amplitude of low-frequency fluctuation (fALFF) of the resting-state fMRI signal to measure the intensity of regional spontaneous activity, and made group by condition comparisons using 'Threshold-Free Cluster Enhancement' (TFCE). To compare within network and across network connectivity for the Executive Control Network (ECN), Salience Network (SN) and the Default Mode Network (DMN), seeds were taken from left and right DLPFC, ACC, PCC as central nodes of the respective networks.

Results: There was decreased dACC activity in hypnosis. In group-level analysis of hypnosis vs. rest throughout the brain, highs showed reduced regional fractional amplitude of BOLD signal in the dACC and left superior frontal gyrus compared with lows in those conditions (TFCE), $p < .05$. There was coupling of EC and Salience Networks. In between-group analysis, the left DLPFC displayed enhanced connectivity to ipsilateral insular cortex and contralateral supramarginal gyrus in highs compared to lows during hypnosis and rest ($p < .05$, corrected for multiple comparisons). The same pattern showed for connectivity between right DLPFC and ipsilateral insula ($p < .001$). For lows, there were no significant differences for the hypnosis-rest contrast with either DLPFC seed. There was decoupling of the EC and DM Networks during hypnosis. Connectivity between left DLPFC and core DM regions, posterior cingulate cortex (PCC) and contralateral inferior parietal lobule (IPL), were significantly negatively correlated with hypnotic experience ratings in all 36 highs during hypnotic scans at $p < .05$. This was also true for right DLPFC and DMN regions.

Conclusions: Here we show for the first time that during hypnosis there is reduced activity in the dorsal anterior cingulate gyrus, increased functional connectivity between the dorsolateral prefrontal (ECN) and the insular and dorsal anterior cingulate cortices (SN), and reduced connectivity between the dorsolateral prefrontal cortex (ECN) and medial frontal and posterior cingulate cortices (DMN). As subjects reported they felt more hypnotized, there was more functional connectivity between the DLPFC and the insula, and the default mode network became increasingly decoupled from both the left and right DLPFC. These changes underlie the focused attention and enhanced perceptual and somatic control that characterizes hypnosis.

Keywords: Hypnosis, fMRI, Cognitive Neuroscience, Resting state.

Disclosure: Nothing to Disclose.

W10. Risk Taking Behavior in Adolescents with Psychosis: Relationship of Laboratory and Real Life Behavioral Measures to Executive Function

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Background: Although their brains are still developing, during adolescence individuals begin to be held responsible for larger social, health, and academic decisions, and to enter situations in which disadvantageous decision making may lead to substantial risk and permanent consequences. However, decision making in adolescents may be limited by factors such as susceptibility to social influences, poor self-regulation, impulsivity, and risk-taking. In patient populations, adults with both schizophrenia and bipolar disorder have been shown to have decision making deficits, but less is known about decision making in adolescents with severe mental illness. Given the observed executive function deficits in individuals with psychosis, we hypothesize that those deficits may contribute to the difficulty with decision making in this population.

Methods: We assessed a sample of healthy adolescents and those with psychosis using both laboratory based and real-life based decision making measures, as well as the MATRICS Consensus Cognitive battery and neuroimaging assessments including resting state fMRI and diffusion tensor imaging (DTI). Real life decision making was measured based on self-reported life events through the CDC's Youth Risk Behavior Surveillance System (YRBSS). Laboratory based decision making was measured using a version of the Balloon Analogue Risk Task (BART) with two balloons, one with a high and one with a low risk of popping.

Results: First, in the healthy control sample (age 8-21), in the BART, the response variability, an index of the executive component of decision making and the ability to use learned information to make consistent responses, showed significant linear improvement with age. In addition, response variability negatively correlated with the Working Memory sub-score of the MATRICS battery such that better working memory was related to less variability. Then we assessed an age matched subset of late-adolescents with and

without psychosis. In the BART, we observed that while across the testing period, healthy individuals were able to learn from the previous trials and inflate the low risk balloon to a larger size than the high risk balloon, psychosis patients did not show the same behavior, consistent with a decrease in the executive component of decision making. Consistent with this, in the measure of real life behavior, we found significantly higher YRBSS Total Risk scores in the psychosis group, particularly the Suicidality, Tobacco Use, and Cannabis Use scales.

Conclusions: We have observed an improvement in the executive component of BART performance with age in healthy adolescents and young adults, which correlated with improvements in a neuropsychological assessment of working memory. In late-adolescents with psychosis, we observed overall higher levels of real-life risk taking than in controls, and a corresponding deficit in learning during a lab based decision making task. These findings support the hypothesis that decision making deficits in adolescents with psychosis may be in part due to executive dysfunction. These results will be further explored as related to neuroimaging measures of structure and function in the executive network.

Keywords: schizophrenia, decision making, adolescence, development.

Disclosure: Nothing to Disclose.

W11. Impaired Response Inhibition and Excess Cortical Thickness as Candidate Endophenotypes for Trichotillomania

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Background: There is an ongoing search in psychiatry for models of the neurobiological circuitry implicated in given disorders. Trichotillomania, an Obsessive-Compulsive Related Disorder, is characterized by repetitive pulling out of one's own hair. Impaired response inhibition has been identified in patients with trichotillomania, along with grey matter density changes in distributed neural regions including frontal cortex. It is not yet known whether cognitive deficits and structural brain abnormalities in trichotillomania are trait or state in nature. The use of an 'endophenotyping' strategy, in which brain structure and function are quantified not only in patients but also in their clinically unaffected first-degree relatives, is a vital first step in addressing the state versus trait issue. A greater understanding of such endophenotypes is likely to have ramifications for neurobiological models, novel treatments and more appropriate diagnostic classification systems. The objective of this study was to evaluate impaired response inhibition and abnormal cortical morphology as candidate endophenotypes for trichotillomania.

Methods: Subjects, aged 18-65 with DSM-5 trichotillomania, were recruited via advertisements and an outpatient psychiatry clinic at the University of Chicago from September 2012 to July 2014. For each subject, a clinically unaffected first-degree relative was also enrolled. Controls with no history of psychiatric disorders were recruited from the community. All participants provided written informed consent. Before undergoing neuroimaging, all subjects underwent a structured clinical interview by a board-certified psychiatrist. Disease severity was assessed using Massachusetts General Hospital Hairpulling Scale (MGH-HPS) and the Clinical Global Impressions Severity Scale (CGI-S). The Stop-Signal Task (SST) was used to probe dissociable neural circuitry and cognitive processes likely to be implicated in the pathophysiology of trichotillomania as it activates distributed circuitry including the right frontal gyrus. Structural MRI scans were processed using FreeSurfer. After cortical reconstruction, cortical thickness was compared between the study groups using permutation cluster analysis with stringent correction for multiple comparisons (cluster-forming threshold of $p < 0.001$, and cluster-wise p value $p < 0.05$, two-tailed). Regions in which subjects and their relatives together differed significantly from controls in cortical thickness were identified. Mean thickness in each identified cluster for each subject was extracted and subjected to post-hoc tests to further explore group differences (Monte Carlo permutation testing). Secondary exploratory correlational analyses (Spearman's r) were used to evaluate relationships between: (a) response inhibition and cortical thickness (in all participants and then in each subgroup); (b) response inhibition and disease severity in the trichotillomania subjects; (c) cortical thickness and disease severity in the trichotillomania subjects; and (d) cortical thickness and age (in all participants and then in each subgroup).

Results: Subjects with trichotillomania ($N = 12$), unaffected first-degree relatives of these patients ($N = 10$), and healthy controls ($N = 14$), were entered into the study. Groups differed significantly in response inhibition, with patients demonstrating impaired performance versus controls, and relatives occupying an intermediate position. Permutation cluster analysis revealed significant excesses of cortical thickness in patients and their relatives compared to controls, in right inferior/middle frontal gyri (Brodmann Area [BA] 47 & 11), right lingual gyrus (BA 18), left superior temporal cortex (BA 21), and left precuneus (BA 7). Patients did not, however, differ significantly from their relatives on cortical thickness in these clusters, with the exception of the cluster comprising right lateral occipital cortex, in which relatives showed significantly greater cortical thickness than patients. Cortical thickness in these clusters did not correlate significantly with response inhibition or age (considered for all subjects together and each group separately), nor were correlations with disease severity in patients (as measured by the MGH-HPS and CGI-S) identified.

Conclusions: Impaired response inhibition and an excess of cortical thickness in neural regions germane to inhibitory control, and action monitoring, represent vulnerability markers for trichotillomania. These findings draw remarkable parallels with candidate endophenotypes identified for OCD. Future work should explore genetic and environmental associations with these biological markers and further delineate their validity as endophenotypes.

Keywords: trichotillomania, cognition, compulsivity, imaging.

Disclosure: This project was funded, in part, by a grant from the Trichotillomania Learning Center to Mr. Odlaug.

W12. Vortioxetine Reduces BOLD Signal during Performance of the N-Back Task in Subjects Remitted from Depression and Healthy Control Participants

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Background: Major depressive disorder (MDD) is associated with a range of cognitive difficulties, including deficits in executive function and working memory. The neural systems responsible for this deficit have previously been investigated using the N-Back task, which showed increased activity in the dorsolateral prefrontal cortex (dlPFC), hippocampus, anterior cingulate (ACC) and precuneus in both currently depressed and remitted patients, relative to controls. Vortioxetine is a multi-modal antidepressant that is thought to act by inhibiting the serotonin [5-hydroxytryptamine (5-HT)] transporter, antagonising the 5-HT3, 5-HT7 and 5-HT1D receptors and acting as a partial agonist at the 5-HT1A receptor. Previous studies have found that vortioxetine improves performance on tasks of cognitive function in depressed patients and in pro-cognitive animal models. The current randomised, placebo controlled, multisite functional magnetic resonance imaging (fMRI) study investigated the neural systems underlying vortioxetine's influence on cognitive performance using the N-Back task in subjects remitted from depression and healthy controls. The hypothesis tested was that vortioxetine would influence the blood-oxygen-level dependent (BOLD) signal within the neural structures previously identified as hyperactive in depressed patients.
Methods: 96 participants were recruited from 3 academic sites in the United Kingdom. These included 48 currently remitted subjects with at least 2 previous episodes of MDD, who reported subjective cognitive difficulties and who had received no treatment for at least six weeks, and 48 healthy control participants. Participants were randomly assigned in a 1:1 ratio to 2 weeks treatment with either vortioxetine 20mg per day or placebo. During the study, participants completed a letter based N-Back task (working memory) while fMRI data was collected at baseline and following 2 weeks treatment. Contrast images comparing BOLD signal during the N-Back task (i.e. 1, 2 or 3-back) vs. a 0-back control condition were generated at baseline and after treatment with vortioxetine 20mg/day. Change in these contrast images between the two time points was then compared between treatment groups. Group level analysis controlled for study site and gender. Predefined regions of interest in the dlPFC, hippocampi, ACC and precuneus were used, with all group level image analyses corrected at the cluster level at $p < 0.05$. fMRI data was analysed using the fMRIB software library (FSL) version 5.05.
Results: In subjects remitted from depression vortioxetine significantly reduced the BOLD signal within the right dlPFC ($p = 0.05$) and left hippocampus ($p = 0.01$). Vortioxetine did not significantly alter activity within the healthy control group. When the subject groups were combined in a single analysis, vortioxetine significantly reduced activity within the right dlPFC ($p = 0.03$) and left hippocampus ($p = 0.03$). Vortioxetine did not influence activity within the right hippocampus, left dlPFC, ACC or precuneus. Using whole brain analysis, across all subjects, vortioxetine was found to reduce activity within the right insula, temporal-occipital fusiform gyrus and bilateral lingual gyri.
Conclusions: Vortioxetine reduced the BOLD signal within the right dlPFC and left hippocampus during completion of the N-Back task. Acute and remitted major depression have previously been associated with increased activity within these regions, suggesting that treatment with vortioxetine may reverse the effects of the disorder within these neurocognitive systems. This raises the possibility that the cognitive effects of vortioxetine seen in patients with major depression may be mediated, at least in part, by effects of the drug on neural systems supporting working memory (executive function).
Keywords: Neuroimaging, Working memory, Depression, Antidepressants.
Disclosure: This study was sponsored and funded by Lundbeck. Michael Browning is employed by both the University of Oxford and P1vital Ltd. He recieved travel expenses from Lundbeck for attending this conference. JF William Deakin in the last 5 years has held grants from Servier, AstraZeneca and P1vital and given talks and/or advice for Servier, Johnson and Johnson, AstraZeneca and Lilley. Fees are paid as reimbursement for his time to the University of Manchester. Catherine Harmer has received consultancy payments from Lundbeck, P1vital and Servier and is a shareholder in P1vital. She is a company director of Oxford Psychologists and holds shares in the same company. Guy Goodwin has held grants from Servier, received honoraria for speaking or chairing educational meetings from Abbvie, AstraZeneca, GSK, Lilly, Lundbeck, Medscape, Servier and advised AstraZeneca, Cephalon/Teva, Lundbeck, Merck, Otsuka, P1Vital, Servier, Shire, Sunovion, and Takeda, holds shares in P1vital and acted as expert witness for Lilly. Gerard R. Dawson is an employee and holds shares in P1vital Limited. Soren Rahn Chrisensen, Klaus Groes Larsen andChristina Kurre Olsen are employed by Lundbeck. Jeppe Buchbjerg was employed by Lundbeck (at study development and initiation) and is now employed by Novartis.

W13. Biological and Clinical Correlates of Resilience in Patients with Schizophrenia: A Cross-sectional Study

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Background: Resilience refers to the process of adapting successfully in the face of significant risk and adversity. We conducted a cross-sectional study to investigate biological and clinical correlates of resilience in patients with schizophrenia.
Methods: Clinically stable outpatients with DSM-IV schizophrenia were included. Subjective resilience was assessed using the Resilience Scale (Wagnild and Young 1993). As potential biomarkers, adrenocorticotropic hormone, cortisol, high-sensitivity C-reactive protein, and brain-derived

neurotrophic factor (BDNF) were measured in blood samples, while alpha-amylase was measured in saliva samples. The following clinical variables were assessed: sociodemographic data, duration of illness (DOI), psychopathology, insight, antipsychotic dosing, drug attitude, hopelessness, internalized stigma, personal and social performance, premorbid adjustment, QOL, and self-esteem. Variables correlating with resilience were investigated using Pearson's correlation or Spearman's rank correlation. Multiple regression analysis was also performed.
Results: 60 subjects were included (mean ± SD age, 45.9 ± 10.0 years; DOI, 18.9 ± 10.6 years; 22 males). Total scores of resilience amounted to 110 ± 25 (range: 46-170, higher scores indicate higher resilience). Correlations between resilience and biomarkers were non-significant. Resilience positively correlated with self-esteem and QOL, and negatively correlated with hopelessness, internalized stigma, and insight. Multiple regression included self-esteem as the only variable (standardized beta-coefficient = .763, R2 = .583).
Conclusions: This study elucidates several clinical correlates of resilience in patients with schizophrenia. Further studies focusing on the biological bases of resilience, cultural influences, and longitudinal investigations are warranted.
Keywords: resilience, stress, BDNF, schizophrenia.
Disclosure: Nothing to Disclose.

W14. The Interaction of Anhedonia and Anxiety in Schizophrenia

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Background: Social dysfunction is common among individuals with schizophrenia. While often attributed to anhedonia, social dysfunction could also result from unrecognized anxiety. Reduced or absent pleasure from the social environment could produce withdrawal and distort perceptions, rendering it incomprehensible, possibly dangerous, and anxiety provoking. Conversely, social anxiety could produce withdrawal and diminish the pleasure of interactions. Alternatively, anhedonia and anxiety may reflect pathology in separate domains that jointly contribute to social deficits. We examined the contributions of anhedonia and anxiety to social function, and used olfactory function to illuminate the neurobiological underpinnings associated with each.
Methods: Anhedonia, anxiety, and social function were assessed in 56 well-characterized schizophrenia cases and 37 healthy controls, along with smell identification and odor sensitivity. The Liebowitz Social Anxiety Scale was used to assess anxiety and avoidance of a broad scope of hypothetical social and performance situations. It is comprised of four scale scores (social fear, performance fear, social avoidance, and performance avoidance) and a total score. The Chapman Scales for Physical and Social Anhedonia assessed deficits in the ability to experience pleasure from typically pleasurable physical stimuli such as food and sex, as well as social pleasure from non-physical stimuli such as talking and exchanging expression of feelings. The Social Function Scale examined seven areas of social functioning: social withdrawal, interpersonal behavior, social activities, recreation, independence in performance, independence in competence, and employment/occupation. Smell identification was assessed with the University of Pennsylvania Smell Identification Test, and odor sensitivity was assessed with the Smell Threshold Test from Sensonics Inc.
Results: Schizophrenia cases exhibited significantly higher levels of anhedonia and anxiety than controls, and the domains were highly correlated in the cases. The combination of anhedonia and anxiety more strongly predicted social dysfunction than either measure alone. Smell identification was differentially related to the domains, with better smell identification predicting less physical anhedonia, but more social fear in male cases. Additionally, among male cases, increased odor sensitivity was related to lesser social anhedonia.
Conclusions: This study demonstrated greater levels of anhedonia and anxiety in a group of schizophrenia cases. The domains of psychopathology were significantly correlated in the cases, and both independently and together, anhedonia and anxiety significantly impacted social function. The interaction between total anhedonia and total anxiety scores on social function was significant in both cases and controls, demonstrating that when heightened, dysfunction in both domains significantly impacts social function. Using smell identification performance as a biomarker for negative symptoms, the domains could be distinguished. Better smell identification predicted less physical anhedonia, but more social fear. These findings suggest that social dysfunction may improve with interventions for anxiety in some schizophrenia cases, even in the presence of anhedonia. As negative symptoms are historically difficult to treat in schizophrenia, identification of and treatment for underlying anxiety has the potential to drastically improve functional outcome in these individuals.
Keywords: schizophrenia, anhedonia, anxiety, olfaction.
Disclosure: Nothing to Disclose.

W15. Opposite Modulation of D2/D3 Receptors in Caudate and Ventral Striatum on Striatal Activation: Disruption in Cannabis Abusers

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Background: Dopamine neurotransmission modulates neuronal activity in: 1) ventral striatum (VS), which receives projections from the ventral medial PFC and is involved in salience attribution, reward and impulsivity; and 2) dorsal caudate (CD), which receives projections from dorsolateral PFC and is associated with control of behavior and cognitive function. The balance between these inputs results in behavioral actions that can lead to impulsive actions or in control and regulation of responses. Recent data highlights significant overlap of cortical projections into striatal regions, with the highest overlap occurring in

the CD. This suggests that optimal performance for certain actions or tasks might require balanced activity among different striatal regions. Here we test the hypothesis that correct task performance reflects striatal fMRI responses differentially and simultaneously modulated by D2/D3 receptors (D2/D3R) in CD and VS. Based on recent work showing that cannabis abusers have blunted reactivity to dopamine stimulation we also hypothesized a disruption in the neurovascular coupling between fMRI signals and D2/D3R in CD and VS in cannabis abusers.

Methods: We evaluated brain activation to a simple sensorimotor (SM) reaction time (RT) task with 4T fMRI and striatal D2/D3R with [11C]raclopride PET in 18 cannabis abusers (CNB; age: 27 years, 9 females) and 14 matched controls (NML: age: 26 years, 5 females). The event-related SM task involved visual perception of circles ('targets') displayed randomly at the corners of the peripheral field of view every 12 seconds (2sec jittering). We measured brain activation with the blood-oxygenation-level dependent (BOLD) contrast and the RT required for the subjects to respond to the presence of a target. SPM8 was used for standard image preprocessing and for BOLD signal estimation, independently for successful ('hits'; $RT < 600ms$) and for unsuccessful ('misses'; $RT > 600ms$) trials, while carefully controlling for head motion and hemodynamic response variability. The average values of the non-displaceable binding potential in each voxel computed from normalized PET images were averaged within CD and VS regions-of-interest based on the Automated Anatomical Labeling digital atlas. SPM8 multiple linear regression (MLR) analysis was used to assess the association between fMRI signals in the striatum and D2/D3R in CD and VS. The statistical significance of the MLR slopes that quantify the neurovascular coupling was set as $Pcorr < 0.05$, corrected for multiple comparisons within the striatum.

Results: Performance accuracy during the SM task showed a negative correlation with age at onset of cannabis use in the CNB group ($R = -0.65$; $P = 0.003$), and with the strength of the fMRI responses in VS ($R = -0.68$; $P = 0.006$) in NML, but not in CNB subjects. Across all subjects, the negative fMRI responses in VS linearly increased with D2/D3R in VS and decreased with D2/D3R in CD for hits ($Pcorr < 0.05$), but not for misses. For hits, the amplitudes of MLR slopes in VS were stronger for the NML than for CNB group ($P < 0.05$). Complementary analyses using the putamen as a control region did not show significant MLR associations in the striatum. This confirmed the specificity of the association between fMRI responses in VS and D2/D3R in CD and VS. The condition number ($k = 28$) and the variance inflation factor ($VIF = 6$) for the MLR model indicated low risk of multicollinearity ($k < 30$ and $VIF < 10$). Cross-validation analysis further demonstrated the robustness of the MLR findings.

Conclusions: We show for the first time that accurate sensorimotor performance, which is associated with VS deactivation, relies on opposite D2/D3R modulation from CD and VS in healthy controls but less so in cannabis abusers. Specifically, D2/D3R in CD had inhibitory effects whereas D2/D3R in VS had excitatory effects on the fMRI signals in VS. This is consistent with the sensorimotor feedback loop and could reflect differential involvement of the direct and indirect pathways. Cannabis abusers demonstrated weaker neurovascular coupling in VS than controls, which could underlie neuroadaptations in striatal circuitry from repeated cannabis intoxication. Cannabis abusers and control subjects, however, showed similar fMRI signals in VS and D2/D3R levels in CD and VS, suggesting that opposing modulation from CD and VS makes the sensorimotor feedback loop robust to between-subjects variability in dopamine neurotransmission.

Keywords: dopamine, striatum, activation, marijuana.
Disclosure: Nothing to Disclose.

W16. State-dependent Enhancement of Neocortical Oscillations in Mice and Humans

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Background: Cognitive symptoms in psychiatric illnesses such as schizophrenia, autism, and depression are associated with impaired network oscillations in neocortex. Non-invasive brain stimulation with periodic stimulation waveforms to enhance oscillatory activity represents an innovative, non-pharmacological treatment. However, little is known about how brain stimulation interacts with ongoing, endogenous network activity. Here we present data from in vitro animal model experiments and human electrocorticography (ECoG) that demonstrates how the effect of periodic stimulation depends on cortical state.

Methods: All animal procedures were approved by Institutional Animal Care and Use Committee of The University of North Carolina at Chapel Hill (UNC-CH). Slices of mouse (Thy1/ChR2) visual cortex were placed on a MEA2100 (Multichannel Systems) and multiunit traces recorded. A 1 Hz oscillation was evoked by squarewave optogenetic stimulation (LED, 460 nm, 200 μW delivered to the slice) for the duration of the experiment. Electric field stimulation was applied for 10 s at the frequency of the oscillation (1 Hz), twice the frequency of the oscillation (2 Hz), and two nearby frequencies (0.8 and 1.2 Hz) with 10s of only optogenetic stimulation before and after each electric field stimulation at 1 Hz. All procedures involving human participants were approved by the Institutional Review Board of UNC-CH and informed consent was obtained. The patient was implanted with FDA-approved AdTech subdural arrays of electrodes covering right frontal and parietal regions for monitoring of the seizure onset zone prior to resective surgery. The research protocol involved stimulating 14 different electrode pairs (1 cm apart) while the patient was asked to rest with eyes closed ("resting state") and while performing a visual working memory task ("cognitive load"). Bipolar electrical stimuli 2 mA in amplitude, 200 μS in duration and 10 Hz in frequency were applied for 5 s with an FDA-approved Grass Technologies Cortical Stimulator. ECoG data was concurrently recorded at 800 Hz using Aura system (Grass Technologies).

Results: To test this hypothesis, we first evoked a 1 Hz cortical oscillation using LED stimulation of layer 5

pyramidal cells (L5 PYRs) in acute cortical slices of Thy1/ChR2 mice. We then applied 10 s epochs of EF stimulation. We observed that regardless of the EF stimulation frequency the frequency preference for the 1 Hz oscillation was enhanced ($p: < 0.001$ for 2 mV/mm at 0.8 Hz, < 0.001 for 2 mV/mm at 1.0 Hz, 0.044 for 2 mV/mm at 1.2 Hz, and < 0.001 for 2 mV/mm at 2.0 Hz, Wilcoxon signed rank with Bonferroni correction; $n = 88$). We then performed experiments without a prominent 1 Hz oscillation and observed 1 Hz frequency preference only for 1 and 2 Hz EF stimulation (p: 1 for 0.8 Hz, < 0.001 for 1.0 Hz, 1 for 1.2 Hz and < 0.001 for 2.0 Hz; $n = 144$). Rather, the networks responded with increased frequency preference for the EF stimulation frequency ($p < 0.001$ for all stimuli, $n = 144$). These results indicate that the ongoing cortical dynamics shape the response to stimulation. We then examined if the same effects are present in humans. Spectral analysis of ECoG data in the 5 s epoch before stimulation revealed high power at $\sim$ 7 Hz during the resting state as well as under cognitive load. However the overall power in lower frequencies was considerably lower under cognitive load ($p < 0.001$, Cohen's $d = 1.01$). During resting state, stimulation at 10 Hz increased power in the endogenous frequency during stimulation ($p < 0.001$, $d = 0.18$). The effect persisted in the epoch after stimulation ($p < 0.001$, $d = 0.10$). There was a slight but not significant increase at the stimulation frequency during stimulation ($p = 0.064$, $d = 0.09$). Interestingly the power at stimulation frequency was lower after stimulation than before stimulation ($p < 0.001$, $d = 0.21$). In the presence of cognitive load, the power at endogenous frequency decreased during stimulation ($p < 0.001$, $d = 0.27$) while the power at stimulation frequency increased ($p < 0.001$, $d = 0.33$). During the epoch after stimulation, power at endogenous frequency was still lower than the power in the epoch before stimulation ($p < 0.001$, $d = 0.35$) while power at stimulation frequency was higher ($p < 0.001$, $d = 0.50$).

Conclusions: Our results demonstrate strikingly similar, state-dependent responses both in our mouse in vitro preparation and our human ECoG study. Together, our data strongly support a view where presence of pronounced endogenous oscillations limits the effects of periodic stimulation to enhancing that oscillation, whereas, in absence of strong endogenous oscillations, stimulation can be used to shift the oscillation frequency. Additionally, we demonstrate the presence of outlasting stimulation effects in humans that are in agreement with successful switch in cortical state by brain stimulation. This mechanism provides important insights on the road towards rational design of adaptive, individualized brain stimulation for the treatment of psychiatric illnesses. Research reported in this publication was supported in part by the National Institute of Mental Health of the National Institutes of Health under Award Number R01MH101547 (FF). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The ECoG study was supported by a UNC Translational Team Science Award to FF and HS.

Keywords: brain stimulation, cortex, oscillation, cognition.

Disclosure: Nothing to Disclose.

W17. Subjective and Psychophysiological Indices During Extinction: Predictors of Treatment Response in Anxious Youth

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Background: Youth with anxiety disorders are commonly treated using exposure therapy. Extinction is the proposed mechanism of exposure therapy; however, very little work has shown a correspondence directly. We examined whether indices of fear conditioning and/or extinction predict treatment response in youth with anxiety disorders.

Methods: Nineteen anxious youth (10.8 ± 2.4 years) completed a differential fear conditioning paradigm followed by extinction. In this paradigm, two women displaying neutral expressions served as the conditioned stimuli (CS). One CS + was paired with the unconditioned stimulus (US), a fearful face terminating with a loud scream. The CS- was not paired. Subjective measures of the CS + and CS- were rated after fear conditioning and fear extinction phases. Psychophysiological measures (e.g., fear potentiated startle, skin conductance) were measured continuously. Afterwards, the anxious youth received cognitive behavioral therapy (CBT). Most individuals also received an attention training augmentation involving active training away from threat or placebo dot-probe training. Anxiety symptoms were measured before and after 8 weeks of treatment via clinician and self-report to assess treatment response. Using Pearson correlations and $\alpha = .05$, we examined the association between subjective and psychophysiological indices of fear conditioning and extinction and treatment response at 8 weeks compared to baseline.

Results: Significant reductions were detected via clinician [baseline Pediatric Anxiety Rating Scale (PARS): 16.4 ± 2.9, week 8 PARS: 11.6 ± 4.3, $p < 0.02$] and self-reported measures [baseline Screen for Child Anxiety Related Disorders (SCARED): 29.9 ± 13.9, week 8 SCARED: 21.1 ± 12.1, $p < 0.001$]. In addition, higher anxiety ratings of the CS- and lower startle response to the CS- during extinction yielded greater symptom reduction based on PARS [$r(18) = 0.58$, $p < 0.011$] and SCARED [$r(16) = -0.52$, $p < 0.04$], respectively.

Conclusions: In this preliminary analysis, several findings are noteworthy. First, subjective and startle responses to the safety cue (CS-) during extinction predicted treatment response. Individuals with poor safety discrimination and lower physiological reactivity to the safe cue (i.e., CS-) showed greater symptom improvement. Second, the self-report measures of the CS- corresponded to clinician-rated treatment response, while psychophysiological measures of the CS- corresponded to self-reported treatment response. Finally, a common measure of fear conditioning and extinction, skin conductance, did not predict symptom reduction. Understanding the association between indices during extinction and treatment response will help improve therapeutic approaches for youth with anxiety disorders.

Keywords: fear conditioning, cognitive behavioral therapy, youth, anxiety.

Disclosure: Nothing to Disclose.

W18. Contributions of Neurons in Macaque Subgenual Anterior Cingulate Area 25 to Risky Choices

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Background: The subgenual anterior cingulate cortex (sgACC) is a poorly understood cortical region. It appears to participate in reward-related cognition, and may serve integrative functions and/or in deployment of executive control. Although there is a clear primate analogue of the human sgACC, very little work has been done to characterize its neuronal responses. Recent deep brain stimulation studies suggest that sgACC may be important for influencing mood and may be linked to depression. Moreover, neuroimaging studies suggest that it may play an important role in drug addiction, although its specific role remains unclear. At a more fundamental level, our understanding of the computational properties of the anterior cingulate cortex are mostly limited to dorsal structures, impeding the formation of a general theory of cingulate function. We recorded activity of single neurons in the sgACC of monkeys performing a novel gambling task. For purposes of comparison, we also recorded activity of neurons in the dorsal anterior cingulate cortex (dACC) in the same task.
Methods: We used standard single-unit methods to record responses of 28 single neurons in the subgenual anterior cingulate cortex (area 25) while monkeys performed a novel gambling task that we called the token gambling task. In separate sessions, we recorded responses of 112 dorsal (i.e. supragenual) anterior cingulate cortex (dACC) neurons. Our task requires monkeys to choose between two risky options that differ in probability of two different rewarding outcomes, a win and a loss (or neutral) outcome. All outcomes were either increases or decrements (or no change) in the number of tokens in the monkeys' token bank. Whenever six tokens accrued into the bank, the monkey obtains a large water reward and number of tokens resets to zero. The monkey also received a small water reward each trial, regardless of gamble outcome, to maintain motivation. Water rewards were aliquots of water delivered orally by a juice tube controlled by a solenoid valve. 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 responses to offers themselves.
Results: We recorded data in 28 sgACC neurons in one subject over 25 behavioral sessions. Behavior was stable and consistent and closely matched that obtained in our dACC recording experiment using the same task. Moreover, patterns of choices were close to reward-maximizing and matched qualitatively those observed in other (non-token) gambling tasks in the past. Specifically, subjects showed consistent risk-seeking patterns and weak trial to trial fluctuations reflecting a win-stay/lose-shift strategy. Moreover, risk-seeking increased as a function of number of tokens, consistent with the idea that monkeys appreciate the token structure and focus on the possibility of a 'large win' (cf. Heilbronner and Hayden, 2013). Neurons in sgACC showed clear sensitivity to task events, indicating a clear task-driving effect. The largest and most consistent responses were outcome monitoring signals. At the population level, neuronal monitoring responses differentiated different outcomes (win vs. loss) and the size of the outcome. Neuronal responses did not generally indicate salience of the outcome (i.e. they did not show a rectified reward size signal). We also found a clear representation of offer amount as well, and some evidence for comparison processes, specifically, value difference signals. Notably we found that offer signals, comparison signals, and monitoring signals were present in individual neurons, suggesting functional overlap in their properties. Overall, we found a high degree of overlap between the function of dACC and sgACC in neuronal responses, consistent with the idea of a unified cingulate function.
Conclusions: We provide the first description of the role of subgenual cingulate cortex neurons in risky choice tasks, and the first direct comparison of function of sub- and supra-genual cingulate neurons. Our data endorse the idea that cingulate cortex plays a single unified function that includes both choice and monitoring aspects of choice. We also find that reward signals in cingulate cortex are more complex and diverse than previously believed, and that reward encoding is not limited to real rewards, but extends to tokens that accumulate to yield real rewards.
Keywords: cingulate, subgenual, area 25, gambling.
Disclosure: Nothing to Disclose.

W19. Neural Mechanisms of Eye Gaze Perception: Implications for Treatment of Schizophrenia

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Background: The ability to process social information accurately and effectively is disrupted in schizophrenia (SZ), severely affecting social functioning. Abnormal processing of eye gaze direction—a ubiquitous social cue—significantly accounts for deficits in broader social functioning in SZ. Previous work suggests two alternative hypotheses: a) A bottom-up model—basic visual processing deficits lead to problematic gaze perception; or b) A top-down model—impaired higher-level processes (e.g., attention) fail to modulate activity in visual cortex, leading to abnormal gaze perception. Identifying where these deficits lie in the processing stream of the brain has important implications for designing therapeutic strategies. In this pilot study, we evaluated the validity of two paradigms to be used in futures studies to test the bottom-up model.
Methods: This study combines psychophysics and fMRI to examine gaze perception and basic visual perception. Gaze perception and visual integration were probed with two psychophysics tasks, the eye-contact perception task (GAZE) and Jittered Orientation Visual Integration Task (JOVI), respectively, during BOLD fMRI. GAZE was presented in a blocked-event-related design, with stimuli of faces with 9 varying gaze directions (from averted to direct in gradual increments). Participants had to indicate by pressing a button whether they feel the face is looking at them (gaze: yes/no), or the gender of the face (gender: male/female). For JOVI, participants were presented an egg-shaped contour formed by Gabor elements embedded in noise, and they had to identify the direction to which the contour is pointing (left/right). Difficulty increases as the jitter degree of the contour-forming Gabor elements increases. Trials were presented in blocks by jitter degree ($0, \pm 7, \pm 9, \pm 11, \pm 13,$ or ± 15), mixed with 10% of

"catch" trials (trials without noise in background or the contour is traced by a line). For GAZE, trial types (gaze, gender) were modeled as regressors to identify the brain regions recruited in gaze processing. For JOVI, jitter angles were modeled as regressors to identify brain regions recruited in visual integration, defining the region of interest in the visual cortex. Pilot data were collected from 12 psychiatrically healthy individuals (age: 39 ± 15; 42% female) to demonstrate the feasibility and efficacy of the tasks. All P values for fMRI results were FWE-corrected.

Results: For GAZE, eye-contact endorsement rate showed a linear pattern respective to eye-contact signal strength: 11%, 8%, 21%, 30%, 48%, 53%, 61%, 82%, and 91%, $F(8,88) = 67.4$, $P < .001$. Gaze processing, relative to gender identification, involved increased BOLD signals in right inferior frontal gyrus/insula ($k = 631$, $P = .001$) and right supramarginal gyrus ($k = 481$, $P = .003$). For JOVI, participants were 99.7% accurate with "catch" trials, and accuracy showed a linear relationship with jitter level: 82%, 78%, 76%, 60%, 58%, and 55%, $F(5,55) = 22.8$, $P < .001$. Compared with the implicit baseline, the task activated a large portion of the visual cortex, especially the middle and lateral occipital gyrus/posterior precuneus/fusiform gyrus ($Z = 5.89$, $P < .001$, $k\neg = 4526$, $P < .001$), right middle/inferior frontal gyrus/insula ($k\neg = 599$, $P < .001$) and left insula ($Z = 4.85$, $P = .037$), and deactivated postcentral gyrus/anterior precuneus/middle cingulate gyrus ($Z = 5.58$, $P = .001$, $k\neg\neg = 5971$, $P < .001$), left inferior parietal lobule/superior temporal gyrus ($k = 674$, $P < .001$), superior frontal gyrus ($k\neg = 1060$, $P < .001$), and angular gyrus ($k\neg\neg = 261$, $P = .019$).

Conclusions: The preliminary results suggested that GAZE and JOVI are effective paradigms for probing gaze perception and visual integration, respectively. Gaze perception activated regions associated with emotional experience (insula) and mentalizing (supramarginal gyrus), consistent with the role of these functions in this social cognitive task. In addition, gaze perception and visual integration showed overlapping neural networks in the occipital cortex and right temporo-parietal regions, supporting the relevance of basic visual processing in social cognition. Collection of more healthy data and SZ data is underway. Future analyses will compare SZ patients and healthy controls for behavioral performance and brain activation during these tasks to identify altered neural circuitry of gaze perception and visual integration in SZ.

Keywords: schizophrenia, social cognition, fMRI, visual perception.

Disclosure: Nothing to Disclose.

W20. Verbal Working Memory in Schizophrenia from Consortium on Genetics in Schizophrenia: Moderating Role of Antipsychotics and Smoking

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Background: Working memory impairment is profound and enduring among schizophrenia patients and has been suggested as a promising candidate for an endophenotype. Although working memory has been extensively studied in schizophrenia, less is known about potential moderators of the impairment. Specifically, the effects of demographic and clinical features on working memory in schizophrenia are poorly understood. With large samples of patients and controls from the Consortium on the Genetics of Schizophrenia case-control (COGS-2) study, this study aimed to investigate the following two research questions: 1) do any of following moderators affect working memory impairment in schizophrenia: cigarette smoking, antipsychotic medication, the interaction between cigarette smoking and antipsychotic medication, and past substance abuse; and 2) do any of the significant moderators identified modulate the relationship between working memory and community functioning in schizophrenia.

Methods: From 5 sites, 1377 patients with schizophrenia or schizoaffective, depressed type and 1037 healthy controls completed the Letter-Number Span (LNS) Task. The LNS task consisted of two conditions: the "Forward" and "Reorder" conditions. Both conditions employed a set of intermixed letters and digits. In the Forward condition, participants were asked to repeat the letters and numbers in the same order as they were presented. In the Reorder condition, participants were asked to repeat the digits in ascending order first and then the letters in alphabetical order. In addition, both patients and controls received the Global Assessment of Function Scale (GAF). Additional clinical assessment for patients included a modified versions of the Scale for the Assessment of Negative Symptoms (SANS) and Positive Symptoms (SAPS), the Brief version of the UC San Diego Performance-based Skills Assessment (UPSA) as a measure of functional capacity, and the Role Functioning Scale (RFS) for community functioning.

Results: Schizophrenia patients performed more poorly than controls, with a larger difference on Reorder than Forward conditions. This difference was not explained by age and parental education differences between groups or across sites. Patients who smoked showed larger impairment than nonsmoking patients, primarily due to deficits on the Reorder condition. Regarding the types of antipsychotic medication, four medication groups (first-generation antipsychotics, second-generation antipsychotics, both first- and second-generation antipsychotics, and no antipsychotic medication) did not differ on the Forward, but patients taking no antipsychotic medication performed better on the Reorder than other medication groups. Further, the impairing association of smoking with LNS performance was more pronounced among patients taking first-generation than those taking second-generation antipsychotic medications. History of substance use did not moderate working memory impairment. Finally, verbal working memory deficits were associated with symptoms, functional capacity, and functional outcome and these associations were stronger for nonsmokers.

Conclusions: In these large samples of patients and controls across 5 sites, verbal working memory impairment was clearly present and larger for patients who currently smoke. The effect of smoking status also interacted with types of antipsychotic medications: the impairing effect of smoking on Reorder was more pronounced among patients taking

first-generation antipsychotics. The greater impairment in smokers may reflect added burden of smoking on general health or that patients with greater deficits are more likely to smoke. Studies with more specific subtypes of working memory tasks instead of a relatively global measure such as the LNS will be able to investigate the underlying mechanisms through which these moderators affect working memory impairment and their clinically important associations to real world functioning.

Keywords: schizophrenia, moderators, working memory, smoking, antipsychotic medication.

Disclosure: Dr. Green has been a consultant to AbbVie, Biogen, DSP, EnVivo/Forum and Roche, and he is on the scientific advisory board of Mnemosyne. He has received research funds from Amgen. Dr. Lazzeroni is an inventor on a patent application filed by Stanford University on genetic polymorphisms associated with depression. Dr. Light has served as a consultant for Astellas, Forum, and Neuroverse. Dr. Nuechterlein has received unrelated research support from Janssen Scientific Affairs, Genentech, and Brain Plasticity, Inc., and has consulted to Genentech, Otsuka, Janssen, and Brain Plasticity, Inc. Dr. Swerdlow has been a consultant for Genco Sciences, Ltd. All other authors declare that they have no conflict of interest.

W21. Disrupted Cognitive Control During Nicotine Withdrawal: Possible Links to BDNF Imbalance in the Frontostriatal Circuits

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Background: Nicotine addiction is a global health problem and smoking-related illness is the largest preventable cause of death. Although smoking cessation produces various somatic and affective signs of withdrawal during first few days of abstinence, withdrawal-related cognitive deficits are considered to be one of the most critical symptoms that predict relapse. Therefore, delineation of cognitive mechanisms that determine the vulnerability to the addictive potential of nicotine is likely to provide gainful insights into the neurobiology of nicotine addiction. The present study was designed to examine the effects of nicotine withdrawal on cognitive control processes in mice. Because the integrity of frontostriatal circuits is critical for executive processes and brain-derived neurotrophic factor (BDNF) modulates plasticity in these circuits, we also assessed the effects of nicotine withdrawal on prefrontal and striatal BDNF expression.

Methods: Male C57BL/6J mice were trained in an operant cognitive flexibility task that required the animals to switch from a visual cue-based discrimination strategy to an egocentric spatial response strategy to obtain a reward. Following autoshaping and attaining pretraining criterion, osmotic minipumps were implanted subcutaneously to deliver either saline or nicotine (18mg/kg/day; base) for 4 weeks. During this period, animals received visual discrimination training. After attaining criterion (80% correct responses for 3 consecutive days), mice remained on this phase of the task until 3 weeks of saline/nicotine treatment was completed. Animals were then randomly assigned to either the precipitated withdrawal or control groups and tested for the acquisition of strategy shifting. Precipitated withdrawal was induced via a subcutaneous injection of mecamylamine, a non-specific nicotinic receptor antagonist (3mg/kg), 20 min. prior to daily testing sessions that continued for seven days. Control groups were challenged with saline and tested for performance in a similar fashion. At the completion of behavioral experiments, brains were analyzed for changes in BDNF protein expression.

Results: One-way ANOVAs showed a significant treatment effect on the trials to criterion in strategy shifting ($F3,27 = 3.96$, $p = 0.02$). Post hoc comparisons revealed that nicotine-treated mice that underwent mecamylamine-precipitated withdrawal required more trials to reach criterion ($p = 0.01$). Subsequent error analyses indicated that slower acquisition was mostly related to these animals' inability to maintain a new learning strategy (learning errors: 17.57 ± 1.49 vs 9.62 ± 2.28 in controls, $p = 0.005$). Interestingly, mecamylamine treatment per se increased perseverative responding to the previously reinforced stimulus. Strategy shifting performance remained unaltered in chronic nicotine-treated animals challenged with saline. The ratio of striatal to prefrontal BDNF levels robustly increased following mecamylamine-precipitated withdrawal as compared to the saline/nicotine-treated animals that were challenged with saline (both $p < 0.01$).

Conclusions: Our findings suggest that the ability to shift strategies in order to maintain goal directed behavior is disrupted during nicotine abstinence. Furthermore, activation of nicotinic receptors is critical for strategy switching, and it is possible that withdrawal-related deficits in executive functions may be related to the recovery of chronic nicotine-induced desensitized state of these receptors. Alterations in activation/desensitization of nicotinic receptors during withdrawal may directly or indirectly produce perturbations in corticostriatal BDNF signaling, leading to deficits in cognitive control processes. As cognitive changes during nicotine abstinence predict relapse, therapeutic strategies aimed at normalizing BDNF imbalance and restoring executive functions may be considered for smoking cessation.

Keywords: nicotine addiction, BDNF, executive functions, prefrontal cortex.

Disclosure: Nothing to Disclose.

W22. Pleiotropic Locus for Emotion Recognition and Amygdala Volume Identified Using Univariate and Bivariate Linkage

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Background: Emotion recognition deficits occur in schizophrenia, bipolar disorder, depression and also in neurodegenerative illness. The amygdala appears to have a preferential role in affect processing in both healthy and

mentally ill individuals. Indeed, the role of the amygdala in emotion recognition is well established and separately each trait has been shown to be highly heritable, but the potential role of common genetic influences on both traits has not been explored. Identifying genes with pleiotropic influence on both traits might reveal those molecular mechanisms that alter brain architecture and/or function, which in turn affect emotion-recognition performance. In so doing important molecular targets might be revealed for targeting emotion-recognition deficits in those individuals suffering from mental and neurodegenerative illness.
Methods: Univariate and bivariate polygenic and linkage analyses were applied to amygdala volume and emotion recognition in a sample of randomly selected, extended pedigrees (N = 858; 115 families, average size 7.53 people, range = 1-89). Genomic regions meeting bivariate genome-wide significance for linkage were investigated in greater detail using association analysis of the emotion and amygdala confirmatory factor score and the genetic variants encapsulated by the linkage peak. Statistical significance levels were established according to the effective number of tested variants given the linkage disequilibrium (LD) structure in the region.
Results: Using a combination of univariate and bivariate linkage we found a pleiotropic region for amygdala and emotion recognition on 4q26 (LOD = 4.34). Association analysis conducted in the region underlying the bivariate linkage peak revealed a variant meeting the corrected significance level (pBonferroni = 5.01x10-05) within an intron of PDE5A (rs2622497, X2 = 16.67, p = 4.4x10-05) as being jointly influential on both traits.
Conclusions: PDE5A has been implicated previously in recognition-memory deficits and is expressed in subcortical structures that are thought to underlie memory ability including the amygdala. The present paper extends our understanding of the shared etiology between amygdala and emotion recognition by showing that the overlap between the two traits is due, at least in part, to common genetic influences. Moreover, the present paper identifies a pleiotropic locus for the two traits and an associated variant, which localizes the genetic signal even more precisely. These results, when taken in the context of previous research, highlight the potential utility of PDE5-inhibitors for ameliorating emotion-recognition deficits in populations including, but not exclusively, those individuals suffering from mental or neurodegenerative illness.
Keywords: Amygdala, Emotion Recognition, Linkage, Association.
Disclosure: Nothing to Disclose.

W23. Conditioned Fear and Extinction Learning Performance and Its Association with Psychiatric Symptoms in Active Duty Marines

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Background: Posttraumatic Stress Disorder (PTSD) is a major public health concern, especially given the recent wars in Iraq and Afghanistan. Nevertheless, despite a sharp increase in the incidence of psychiatric disorders in returning veterans, empirically based prevention strategies are still lacking. To develop effective prevention and treatment strategies, it is necessary to understand the underlying biological mechanisms contributing to PTSD and other trauma related symptoms.
Methods: The "Marine Resiliency Study II" (MRS-II; Oct 2011-Oct 2013) Neurocognition project is a longitudinal investigation of neurocognitive performance in Marines deployed to Afghanistan. As part of this investigation, 1,195 Marines and Navy corpsmen underwent a fear conditioning and extinction paradigm and psychiatric symptom assessment prior to deployment. The current study assesses 1) the effectiveness of the fear potentiated startle paradigm in producing fear learning and extinction in this population, and 2) the association of performance in the paradigm with baseline psychiatric symptom classes (Healthy, PTSD symptoms, Anxiety symptoms, and Depression symptoms).
Results: The task was well tolerated and very effective in producing differential fear learning and fear extinction in the Marine participants. Further, distinct patterns emerged differentiating the PTSD and Anxiety symptom classes from both Healthy and Depression classes. In the fear acquisition phase, the PTSD group was the only group to show deficient discrimination between the conditioned stimulus (CS+) and safety cue (CS-), exhibiting significantly larger startle responses during the safety cue compared to the healthy group. During extinction learning, the PTSD group showed significantly less reduction in their CS+ responding over time compared to the healthy group, as well as reduced extinction of self-reported anxiety to the CS+ by the end of the extinction session. Conversely, the Anxiety symptom group showed normal safety signal discrimination and extinction of conditioned fear, but exhibited increased baseline startle reactivity and potentiated startle to the CS+ and CS-, as well as higher self reported anxiety to both cues. The Depression symptom group showed similar physiological and self-report measures as the healthy group. Regression analysis of safety signal learning and extinction performance also indicated that these are orthogonal measures of fear processing across the sample.
Conclusions: These data are consistent with the idea that safety signal discrimination and fear extinction learning are relatively specific markers of PTSD symptoms compared to general anxiety and depression symptoms. These markers may also have distinct underlying mechanisms given their lack of association in this large data set. Further research is needed to determine if deficits in fear inhibition vs. exaggerated fear responding are separate biological "domains" across anxiety disorders that may predict differential biological mechanisms and possibly treatment needs. Future longitudinal analyses will examine whether poor learning of safety signals provides a marker of vulnerability to develop PTSD or is specific to symptom state.
Keywords: PTSD, Fear Extinction, Startle, Anxiety.
Disclosure: Dr. Risbrough has research grant funding from Johnson and Johnson.

W24. Depressed Patients Show fMRI Activity Alterations in Cognitive Control and Valuation Systems when Reappraising Negative Statements

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Background: The effectiveness of cognitive behavioral therapy is testament to the effectiveness of reappraisal in regulating emotion. The brain systems involved in reappraising self-relevant thoughts, however, are not fully understood. Most neuroimaging studies of emotion regulation have typically asked participants to reappraise the valence of negative images with no clear connection to the patient. We examined brain activation during a novel task in which healthy controls and patients with major depressive disorder either listened to or reappraised negative and neutral statements.
Methods: Subjects consisting of 19 controls (age: 34 ± 10 years, Hamilton Depression Scale: 1.11 ± 1.36, 16 female) and 43 patients with major depressive disorder (age: 32 ± 8 years, Hamilton Depression Scale: 20.52 ± 4.70, 32 female) performed an emotion regulation task during BOLD fMRI scanning at 3 Tesla. The task included three conditions: listening to neutral or mildly positive statements (e.g., "you are decent"), listening to negative statements (e.g., "you are dreadful") and reappraising negative statements. The BOLD images were motion corrected, censored of high-motion volumes, coregistered to the T1, resampled to 2-mm isotropic voxels, and spatially normalized. We then regressed each voxel's time course against the experimental conditions and computed contrast coefficients for listen-negative versus listen-neutral and reappraise-negative versus listen-negative. Coefficient maps were smoothed with a 6-mm full-width-at-half-max Gaussian kernel and submitted to t-tests comparing depressed patients versus controls. Maps were thresholded at $p < 0.005$ (uncorrected). In an ROI analysis of the amygdalae, we set a minimum cluster size of 6 voxels for a cluster-wise $p < 0.05$; in a follow-up analysis of the whole brain, we set a minimum cluster size of 81 voxels, for the same cluster-wise p. We examined the interaction contrasts (reappraise-negative versus listen-negative $\times$ depressed versus control, and listen-negative versus listen-neutral $\times$ depressed versus control) as well as the one-way task contrasts in the two groups.
Results: The ROI analysis revealed a crossover interaction in the left amygdala. Controls showed a significant reduction in left amygdala activity during reappraisal, whereas patients showed no change. The whole-brain analysis revealed a similar cross-over pattern in the left inferior frontal gyrus (LIFG), with controls showing decreased activity for reappraisal and depressed patients showing increased activity. In the listen-negative versus listen-neutral contrast, depressed patients increased activity in the dorsal anterior cingulate cortex (dACC) from listen-neutral to listen-negative, whereas controls decreased activity in that region; however, depressed patients also exhibited an overall increase in dACC activity regardless of condition.
Conclusions: When trying to regulate their emotions rather than simply listening to negative statements about themselves, depressed patients more than controls engaged LIFG, a region widely implicated in selection and inhibition processes. However, they did not successfully reduce amygdala activation, perhaps indicating that their exercise of cognitive control was insufficient to blunt the sting of the negative statements. Additionally, when listening to negative rather than neutral statements, depressed patients activated dACC more than did controls. A rich vein of work implicates dACC in signaling response conflict, or a need for more cognitive control, consistent with the greater activation in control-related regions during regulation. Collectively, the regions engaged by our new task partially overlap those reported in the literature on regulating emotional responses to negative pictures, in particular those regions involved in cognitive control and negative valuation.
Keywords: depression, emotion regulation, fMRI.
Disclosure: Nothing to Disclose.

W25. A Meta-analysis of Brain-derived Neurotrophic Factor Effects on Brain Volume and Neurocognition in Schizophrenia

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Background: The regulatory effects of brain-derived neurotrophic factor (BDNF) on neurogenesis, neuronal growth, synaptogenesis, synaptic strengthening, and efficiency portend a downstream effect on brain volume and neurocognition. Studies suggest that the BDNF Val66Met (rs6265) polymorphism is associated with the incidence of schizophrenia and neuroimaging and neurocognitive phenotypes. These associations appear to be however somewhat mixed. A demonstration of the association of BDNF with brain volume and neurocognition at the levels of genetic variation and neurochemical expression would establish BDNF as necessary for understanding changes in structural abnormalities and neurocognition in people with schizophrenia.
Methods: We conducted two separate meta-analyses to investigate the association of BDNF with brain volume and neurocognitive functioning in schizophrenia. Study 1 focused on neurocognitive phenotypes. We examined the association between the Val66Met polymorphism and several neurocognitive phenotypes in people with schizophrenia to provide a quantitative index of differences between Met carriers and Val homozygotes across several studies. Next we examined the association between peripheral expression of BDNF and neurocognitive phenotypes. In Study 2, we conducted a meta-analysis of brain volume differences between Met allele carriers and Val homozygotes. We examined differences focused mostly in frontal and medial temporal structures. There were too few studies to examine the association of BDNF peripheral expression with brain volume.
Results: In Study 1, we found small but statistically significant differences between Met allele carriers and Val

homozygotes on only tasks of visual and verbal learning. There were no significant differences on any other neurocognitive phenotype. Correlations between peripheral BDNF and neurocognitive phenotypes were minimal but we obtained significant effects for the reasoning and problem-solving domains. In Study 2, the association of the Val66Met SNP with hippocampal volume was more robust with average differences between Met carriers and Val homozygotes falling in the small range. Met allele carriers generally demonstrated smaller hippocampal volume than Val homozygotes. The majority of the studies included in the meta-analyses used small samples of schizophrenia patients and there was evidence of significant heterogeneity across studies in the association of Val66Met with neurocognition and brain volume.
Conclusions: In Study 1, we found small but statistically significant differences between Met allele carriers and Val homozygotes on only tasks of visual and verbal learning. There were no significant differences on any other neurocognitive phenotype. Correlations between peripheral BDNF and neurocognitive phenotypes were minimal but we obtained significant effects for the reasoning and problem-solving domains. In Study 2, the association of the Val66Met SNP with hippocampal volume was more robust with average differences between Met carriers and Val homozygotes falling in the small range. Met allele carriers generally demonstrated smaller hippocampal volume than Val homozygotes. The majority of the studies included in the meta-analyses used small samples of schizophrenia patients and there was evidence of significant heterogeneity across studies in the association of Val66Met with neurocognition and brain volume.
Keywords: Brain-Derived Neurotrophic Factor, Schizophrenia, Neurocognition, Brain Volume.
Disclosure: Nothing to Disclose.

W26. Resting State Brain Activity Predicts Prosocial Reciprocity Behavior Towards Others

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Background: The reciprocation of trust is a central element of societies and to the formation and consolidation of interpersonal relationships. For these reasons, understanding how humans make prosocial and self-centered decisions in dyadic interactions and also how to predict these decisions has been an area of great interest in social neuroscience. A functional magnetic resonance imaging (fMRI) based technology with potential immediate clinical application is the study of resting state brain networks connectivity. Resting-state fMRI is obtained while participants lie awake in the MRI scanner without engaging in overt tasks. We hypothesized that the use of resting state fMRI may predict choice behavior in a social context.
Methods: Twenty-nine healthy young adults (25.1 ± 2.3years, 18 female) underwent fMRI while performing the Trust Game, a two person monetary exchange game. We used resting-state fMRI acquired during the same MRI session, demographic characteristics, and a measure of moral development, the Defining Issues Test (DIT-2), to predict an individuals' decision to reciprocate money during the Trust Game.
Results: Subjects reciprocated 74.9% of the time. Independent component analysis identified seven neural networks consistently represented during rest and task. Increased functional connectivity between the salience and the central executive networks correlated with the choice to reciprocate prosocial behavior ($R2 = 0.20$, $p = 0.015$). Multiple regression analysis showed that functional connectivity between the salience (bilateral insula and anterior cingulate) and the frontoparietal (dorsolateral prefrontal cortex and posterior parietal cortex) networks ($p = 0.002$), age ($p = 0.007$) and personal interest schema-a preeminent pattern of decision making focused on what will benefit or help directly the individual-score in the DIT-2 ($p = 0.032$) explained approximately half of the variance in the choice whether to reciprocate or not ($R2 = 0.498$, $p = 0.001$).
Conclusions: Resting state functional connectivity between known neural networks in conjunction with other individual characteristics may be a valuable tool to predict performance in social interactions. Future replication and temporal extension of these findings may be valuable in the clinical, finance and marketing arenas.
Keywords: resting state, behavior predictor, social neuroscience.
Disclosure: This work was partially supported by the Ethics and Community Program from the Arsht Foundation.

W27. Estradiol Improves Performance on Hippocampal Cognitive Tasks in Women Who Report Cognitive Change after Menopause

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Background: Epidemiologic studies suggest that exposure to estradiol (E2) in the early years after menopause is associated with reduced risk of being diagnosed with dementia/Alzheimer's disease in later life. However, interventional studies such as the Women's Health Initiative show that administration of estrogen/progestins non-selectively to older postmenopausal women may increase the risk of dementia. Subjective cognitive complaints in later life are associated with an increased risk of dementia, but the question of whether women who report cognitive problems might benefit from E2 supplementation in the early years after menopause (during the "critical period") has not been answered. We examined the effects of E2 on cognitive functioning in a group of women who report significant cognitive changes after menopause.
Methods: Forty two normal early postmenopausal women were cognitively and behaviorally screened and classified as cognitive complainers (CC; $n = 21$, Age: 56.3 ± 2.9) if they endorsed more than 20% of cognitive symptom items in an extensive self-report battery validated in a study of subjective cognitive impairment, or non-complainers (NC; $n = 21$, Age: 55.5 ± 3.1) otherwise. Both groups exhibited

normal psychometric performance for age. Subjects were scanned (structural and fMRI), cognitively tested at baseline, and then administered 1 mg of oral 17-β estradiol or placebo daily for 3 months. Follow-up scanning and testing then took place, followed by anti-cholinergic drug challenges (reported elsewhere). Subjects were tested with the Selective Reminding Task (SRT) for verbal episodic memory, and spatial navigation utilizing the computerized Virtual Morris Water Maze (VMWM) task.
Results: On the SRT, CC women's total immediate recall was significantly improved after E2 treatment compared to NC women ($p = .018$), whose total recall declined after treatment. Recall failure and recall consistency were unchanged. The CC women also showed significantly improved long-term verbal recall after E2 treatment, while NC women did not ($p = .028$). In the VMWM task, E2 treatment improved platform latency performance during the learning phase in the CC group ($p = .025$) compared to the NC group.
Conclusions: This study provides evidence that E2 may enhance hippocampally-mediated cognitive performance in women who note postmenopausal changes in cognition but not in women without cognitive complaints. E2 may thus have promise for maintenance/improvement of cognitive functioning after menopause in a subgroup of potentially higher-risk women.
Keywords: estradiol, menopause, hippocampus, cognition.
Disclosure: Nothing to Disclose.

W28. Frontal P3 Event-related Potential and Gamma Oscillations are Related to Brain Glutamine/Glutamate Ratio Measured in Vivo

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Background: Deficits of the auditory P3 ERP and the evoked auditory steady-state response (ASSR) at 40 Hz are robust neurobiological abnormalities in schizophrenia (SZ). Animal and drug challenge studies suggest that glutamate neurotransmission plays an important role in modulating P3 ERP and that generation of gamma oscillations depend critically on the interplay between excitatory glutamate and inhibitory γ-aminobutyric acid (GABA) neurotransmitters. However, while direct links between glutamate concentration and P3 ERP and between GABA concentration and gamma ASSR response in humans are suspected, mechanistic details remain largely unknown. We investigated the relationships between P3 ERP, evoked 40 Hz ASSR, glutamate, and GABA concentrations measured in vivo with proton magnetic resonance spectroscopy (1H MRS). We hypothesized that for the P3 ERP, higher glutamate concentrations (Glutamine/Glutamate ratio) in the anterior cingulate (ACC) and in the posterior-occipital (POC) cortices would associate with larger frontal P3a and parietal P3b amplitudes, respectively. For the 40 Hz ASSR, higher GABA and glutamate levels would correlate with larger evoked ASSR in the ACC.
Methods: Frontal P3a (Fz) and parietal P3b (Pz) were collected from 32 healthy participants who performed an auditory oddball task. ASSR phase locking responses at Fz were collected using trains of clicks presented at 40 Hz. Resting GABA and glutamate concentrations (Gln/Glu ratio) were obtained on a 4 Tesla MR scanner and measured using MEGAPRESS and J-resolved methods, respectively. Linear regression and partial correlations were used for statistical analysis.
Results: Controlling for age, grey matter volume, and the time difference between EEG and MRS testing dates (< 100 days), a significant positive correlation was found between frontal P3a amplitude and Gln/Glu ratio in the ACC (partial $R = 0.52$; $P = 0.004$). Relationships between parietal P3b and the Gln/Glu ratio in the POC and between 40 Hz ASSR phase locking and GABA level were not significant. Restricting analyses to participants who had both MRS and EEG measured within 30 days ($n = 16$), we found significant correlations between frontal P3a amplitude and Gln/Glu ratio in the ACC (partial $R = 0.63$; $P = 0.02$) and between ASSR phase locking response and Gln/Glu ratio in the ACC (partial $R = 0.56$, $P = 0.036$).
Conclusions: These results indicate a specific connection between glutamate neurotransmitter concentration in ACC and scalp recorded frontal P3a and gamma responses, providing a novel insight into the relationship between the neurochemical and neurophysiological processes underlying normal cognition. Results are consistent with animal and drug challenge studies that glutamate neurotransmission may be the underlying substrate for P3 and gamma generations. Abnormalities in glutamate neurotransmission have been observed in SZ and may explain illness related deficits of P3 and ASSR.
Keywords: Event-Related Potential, Gamma Oscillations, proton magnetic resonance spectroscopy, glutamate.
Disclosure: Nothing to Disclose.

W29. Default Mode Network Connectivity and Familial Risk for Depression

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Background: Though pharmacotherapy is effective in treating Major Depressive Disorder (MDD), clinical trials indicate that more than half of patients either fail to remit or drop out of treatment prematurely. Even in those who respond to treatment, significant impairments including underemployment and disproportionate levels of medical illness persist. An alternative approach to curtail the burden of MDD is to enhance prevention. Advancing prevention of MDD, however, hinges upon identifying robust biomarkers predictive of the development of the disorder. Research into the pathophysiology of MDD has focused largely on individuals already affected by MDD. Studies have thus been limited in their ability to disentangle effects that arise as a result of the disorder from antecedents of the disorder. By focusing our research on individuals at risk for developing MDD, we have tried to circumvent this limitation. In the current study, we extended this line of inquiry using resting-state functional connectivity MRI

(rs-fcMRI) analysis. In individuals at high and low familial risk for depression, we examined the connectivity of the default mode network (DMN), a collection of brain regions that reliably deactivate during goal-directed behaviors. We focused on the DMN because prior studies suggest functional and connectivity abnormalities of the DMN in depressed individuals. No prior studies, however, have examined whether DMN dysconnectivity precedes the development of MDD, and thus it is unknown whether DMN dysconnectivity represents a biomarker predictive of depression.
Methods: Participants. Complete details on the familial depression study have been reported previously. Risk status for depression was defined based on the first generation (G1), such that offspring (G2 & G3) were classified as high risk if G1 had a history of MDD, and were otherwise classified as low risk. For the current study, MRI scans were obtained from the descendants of G1, consisting of 106 individuals from G2 and G3, ages 11 - 64 (mean = 37.2; SD = 14.3). Of these participants, 58 comprised the high risk group, and 48 the low risk group. Participants were group matched on sex and age and all were Caucasian. MRI Pulse Sequences. High-resolution, T1-weighted and axial echo-planar images were acquired. For resting-state images, participants were instructed to remain still with their eyes closed and to let their minds wander freely. Two 5-minute resting-state scans were obtained for each participant. Image Processing. Standard preprocessing was employed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm). For each participant, independent component analysis and a hierarchical partner-matching algorithm isolated a network of regions corresponding to the DMN. Hypothesis Testing. To test the hypothesis that high vs. low risk participants would demonstrate increased DMN connectivity, we used a random effects linear model with each participant's DMN connectivity map as the dependent variable and group as the independent variable. Age, sex, and history of depression, anxiety, or substance use disorder were covariates. Gaussian Random Field theory was employed for multiple comparison correction ($p < 0.05$, corrected).
Results: Hypothesis Testing. Functional connections within the brain's DMN were greater in individuals with high vs. low risk for depression ($p's < 0.05$, corrected). Increased DMN connectivity was detected in the high risk group within DMN regions including the precuneus and left lateral parietal cortex. There were no regions with greater DMN connectivity in the low risk group. In both groups, we detected negative connectivity (i.e. inverse correlations) between the DMN and regions within the task-positive network (TPN) including the dorsolateral prefrontal, anterior cingulate, and insular cortices. The magnitude of the DMN-TPN negative connectivity was weaker in the high risk group at the dorsolateral prefrontal bilaterally ($p's < 0.05$, corrected). There were no regions with weaker DMN-TPN negative connectivity in the low risk group. Controlling for current or prior depressive, anxiety, or substance use disorders did not meaningfully alter the findings, nor did excluding participants with a current or lifetime history of MDD. Exploratory Analyses. Path analysis indicated that the relationship between familial risk and impulsivity (as determined by commission scores on the Continuous Performance Task) was mediated by DMN-TPN connectivity (indirect effect of family history on impulsivity: coefficient = 0.8 $p = 0.033$).
Conclusions: We found that relative to individuals at low familial risk for MDD, those at high risk had increased DMN connectivity as well as attenuated DMN-TPN negative connectivity. These findings were evident even after excluding participants with a current or lifetime history of MDD, suggesting that these findings are antecedents, rather than the consequence of MDD. Exploratory analyses suggested that DMN-TPN connectivity in high-risk individuals was related to heighted impulsivity. This points to a potential mechanism by which altered connectivity may confer risk for MDD. In conclusion, DMN and DMN-TPN connectivity may offer potential biomarkers predictive of the development of MDD.
Keywords: Depression, Default Mode Network, Functional Connectivity.
Disclosure: Nothing to Disclose.

W30. Kynurenines and Insulin Resistance: Implications for Cognitive Impairment

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Background: Insulin resistance (IR) and type 2 diabetes (T2D) are highly associated with conditions characterized by cognitive impairment, such as depression, schizophrenia, vascular and Alzheimer's type dementias, Parkinson's disease, viral infection (HIV and Hepatitis C virus), and aging. Mechanisms of association between IR (T2D) and these conditions remain unknown. Chronic inflammation and up-regulation of kynurenine (KYN) pathway of tryptophan (TRP) metabolism were reported in these conditions. Considering that KYN, kynurenic acid (KYNA) and their downstream metabolites, 3-hydroxyKYN (3-HK) and 3-hydroxykynurenic acid (3H-KYNA), induce an apoptosis of pancreatic beta-cell and impair biosynthesis, release and activity of insulin, we suggested that inflammation-induced up-regulation of TRP-KYN metabolism is one of the mechanisms of IR development and progression from IR to T2D [1,2].
Methods: As a preliminary step in checking out our suggestion, we evaluated serum concentrations of TRP, KYN, KYNA and IR (HOMA-IR and HOMA-beta) in 60 chronic HCV patients considered for the treatment with IFN-alpha. Study was approved by Tufts Medical Center IRB.
Results: Serum KYN and TRP (but not KYNA) concentrations correlated with HOMA-IR and HOMA-beta scores ($r = 0.32$ and 0.30, resp., $p < 0.01$).
Conclusions: Our finding of correlation between TRP and KYN with IR supports the notion of involvement of up-regulated TRP-KYN pathway in mechanisms of IR and T2D. Our data warrant further studies of downstream KYN metabolites (3-HK and 3H-KYNA) in relation to IR in neurodegenerative disorders. [1]Oxenkrug G. Mol Neurobiol. 2013, 48: 294-301. [2]Oxenkrug G, Ratner R and P. Summergrad. Journal of Bioinformatics and Diabetes, 2013; 1:1-10 Supported by NIMH 104810.

Keywords: kynurenines, insulin resistance, aging, cognition.
Disclosure: Nothing to Disclose.

W31. Reproductive Aging Modulates Working Memory-related Neural Activity in Women

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Background: A rapidly growing body of work from rodents and nonhuman primates has established estradiol's influence on synaptic organization within memory circuitry, including the prefrontal cortex (PFC). Consistent with these findings, previous work from our group demonstrated significant estradiol-dependent effects on dorsolateral PFC fMRI BOLD and working memory performance in young women. Given estradiol's regulation of memory circuitry, the loss of ovarian estrogens during reproductive aging likely plays a significant role in shaping age-related neural changes in mid-life.
Methods: To investigate this, healthy mid-life men and women ($N = 132$; age range 46-53) who are part of a prospective prenatal cohort were enrolled in a population-based follow-up fMRI study. Menstrual cycle histories in conjunction with fasting serum samples collected on the morning of the scan (0800h) were used to determine the menopausal status of women per STRAW-10 guidelines (i.e. late reproductive, menopausal transition, or early post-menopausal, henceforth referred to as "premenopause" "perimenopause" and "postmenopause", respectively). Participants performed a visual working memory task during fMRI scanning. fMRI data were analyzed in SPM8. Statistical maps representing areas with linear increases in activity across memory load (2-back > 0-back) were generated at the random effects level ($p < 0.001$).
Results: Chronological age did not vary appreciably between groups [premenopause (mean, SD; 49.2, 1.6); perimenopausal (49.7, 1.7); postmenopausal (50.1, 1.8)], ($F = 1.29$, $p > .25$). However, LC-mass spectrometry and immunoassay results confirmed that serum estradiol levels declined ($F = 9.22$, $p < 0.001$) and FSH levels rose ($F = 36.76$, $p < 0.001$) significantly as a function of reproductive aging. Next, functional MRI results revealed robust changes in PFC (left middle frontal gyrus, BA9) and posterior parietal cortex (left BA7) BOLD signal during reproductive aging. Postmenopausal women showed greater task-evoked activity compared to both perimenopausal (left MFG/BA9, $p < .001$) and premenopausal (left MFG (BA9), $p < 5x10\text{-}4$; left posterior parietal, $p < .005$) women. Similarly, perimenopausal women showed early signs of exaggerated DLPFC activity compared to premenopausal women (left MFG (BA9/46), $p < .01$). These results are consistent with our previous work in young women, which found greater working memory DLPFC activity under low versus high estradiol conditions (despite indistinguishable performance), a putative marker of neural inefficiency. We see a similar inefficient DLPFC and posterior parietal response in mid-life as ovarian estrogen levels decline and FSH levels rise, despite minimal variance in chronological age.
Conclusions: These data underscore the importance of studying adults early in the aging process in order to understand sex-specific mechanisms that may shape cognitive aging trajectories and, ultimately, disease-risk. Preclinical findings suggest that estrogen therapy may promote healthy cognitive aging, but this is discrepant with many population-level findings (eg. WHI). Examining the hormonal regulation of memory circuitry within a cognitive neuroscience framework may help resolve descrepancies between basic animal and clinical research findings. In a large-scale population-based fMRI study of early aging, our results suggest that loss of ovarian estrogens during menopause plays a significant role in shaping memory circuitry function.
Keywords: aging, estradiol, working memory, fMRI.
Disclosure: Nothing to Disclose.

W32. Do Schizophrenia Patients Show Aberrant Salience Signaling in Observational Environments?

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Background: The aberrant signaling of salience has been proposed as a mechanism of delusion formation in schizophrenia (SZ), and a growing body of evidence has emerged in support of this hypothesis. Salience, however, can take many forms in task environments, and may refer to outcomes that are unexpected, called reward prediction errors (RPEs), and also cues associated with uncertain outcomes. Furthermore, salient stimuli may have "incentive" value (motivating approach behavior), or not. Previous researchers (Walter et al; 2009, 2010) have identified abnormal responses patterns in the ventrolateral prefrontal cortex (VLPFC)/anterior insula (AI), in association with the processing of unsigned RPEs - outcomes that are either more or less rewarding than expected. The AI has been identified as the hub of a salience network (SN) in the brain, and additional research (Palaniyappan et al., 2013) has provided evidence of aberrant spontaneous organization of the SN in SZ. However, several authors (Waltz et al., 2009; Dowd and Barch, 2012) have reported the intact signaling of RPEs in medicated SZ patients, especially in the context of passive tasks, where participants are not required to modify behavior based on the occurrence of unexpected outcomes. Our goal was to test if patients showed intact signaling of RPEs and other forms of salience in the context of a passive RPE-signaling task.
Methods: We acquired event-related MRI data (64 x 64 matrix; FOV = 22 x 22 cm; TR = 2 s; TE = 27 ms; FA = 80°; 4-mm oblique axial slices, 30° axial to coronal) from 17 SZ patients and 20 controls during the performance of a passive outcome prediction task. The task took the form of a card game that participants observed, with the number of blue and red triangles on a card indicating the likelihood of winning a dollar coin. Participants were told that someone (whom they could not see) was playing the game for them, and that they could only predict the outcome (coin or no coin) and not influence it. In actuality, a card with 3 blue and 0 red triangles was followed by a coin 80% of the time,

while a card with 3 red and 0 blue triangles was followed by a coin 20% of the time. A card with 2 blue and 1 red triangle was followed by a coin 60% of the time, while a card with 2 red and 1 blue triangle was followed by a coin 40% of the time. Participants were not explicitly told the contingencies beforehand, but learned the relative expected values of cues through a pre-scanning training session. Participants completed 4 runs of 90-trials, each involving the acquisition of 258 volumes (about 8.5 minutes). Following standard preprocessing of data, functional datasets for individual subjects were submitted to general linear models using AFNI (Cox, 1996). Each of the 8 cue-outcome combinations was represented as a separate regressor of interest. For group analyses, we performed whole-brain analyses using multivariate models (the AFNI 3dMVM function; Chen et al., 2014). Subsequent regions-of-interest (ROI) analyses were performed in a priori ROIs, taken from the literature. These regions included ventral striatum (VS), dorsal striatum (DS), AI, and inferior parietal lobule (IPL), bilaterally, anterior cingulate cortex (ACC), and dorsomedial prefrontal cortex (DMPFC).
Results: Whole-brain analyses revealed main effects of unexpected reward omission in VS and DS, bilaterally, ventromedial PFC, VLPFC, R IPL, and R PHG. Regions showing a main effect of unexpected reward delivery included dorsolateral PFC, bilaterally, R precentral gyrus, and R IPL. Regions-of-interest analyses revealed main effects of unsigned RPE magnitude in bilateral AI, bilateral IPL, and DMPFC in the entire sample, with unexpected rewards and unexpected reward omissions evoking the greatest BOLD-signal activations. These same regions also showed main effects of outcome uncertainty, with cues associated with the more uncertain outcomes (cards with 1 or 2 blue triangles) evoking the greater activations than cues associated with the more certain outcomes (cards with 0 or 3 blue triangles). Importantly, no group differences were observed in any of the ROIs associated with RPE-signaling (VS or DS), or any of the ROIs activated by salient cues or outcomes (AI, IPL, or DMPFC). Group differences were, however, observed in anterior medial PFC, a hypothesized default mode network (DMN) node deactivated by salient events, with SZs showing reduced deactivation of this area.
Conclusions: Our results suggest that, in an observational environment, patients with SZ may show an intact ability to activate striatal and cortical regions involved in the signaling of rewarding and non-rewarding salient events. By contrast, numerous findings of aberrant salience signaling in SZ patients, in the context of operant tasks, suggest that VS and AI responses to salient events in SZ patients may be particularly disrupted when events have motivational salience - implications for behavioral modification. Finally, our observation of reduced deactivation of a hypothesized DMN node in SZs, following salient events, suggests that abnormalities in schizophrenia may particularly affect interactions of the SN with other brain networks, such as the DMN. Supported by National Institutes of Health (NIH) grants K12 RR023250, R01 MH080066, a project grant from HHSN271200599091C/ADB Contract # N01DA-5-9909 and by the National Institute on Drug Abuse - Intramural Research Program (NIDA-IRP).
Keywords: Salience, Reward, striatum, insula.
Disclosure: Nothing to Disclose.

W33. Altered Self-perceptions in Adolescents with Major Depressive Disorder

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Background: Altered self-perceptions are characteristic of major depressive disorder (MDD), often manifesting as feelings of worthlessness and low self-esteem. However, self-perception is highly variable even among depressed individuals. To date, sparse research has accounted for the individual inter-variability differences in biological research of MDD. Here, we sought to investigate self-perceptions in adolescent MDD—early in the course of illness—using both categorical and dimensional analyses.
Methods: Subjects: Twenty-four psychotropic medication-free adolescents with MDD and 19 matched healthy controls (HC) were enrolled and scanned. All were diagnosed using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (KSADS-PL). Word Task: Subjects were presented with positive or negative trait adjectives (e.g., calm, intelligent, likeable, kind, obnoxious, messy, greedy, dumb) and were asked to answer one of three types of questions: (1) self-judgments ("Does this describe you?"); (2) general-judgments ("Is this a good trait?"); (3) letter-judgments ("Is there a letter E?"). Each trial began with 500 ms of fixation, followed by a trait adjective for 3500 ms, and then a 500 ms intertrial-interval (ITI). Subjects responded yes or no about the trait adjective during the 3500 ms presentation. The study was comprised of 2 runs, each beginning and ending with 24 sec of fixation and consisting of 6 blocks of trials (3 categories of trials x 2 blocks). For each block, the subject first viewed instructions for 4 sec and then was pseudo-randomly presented with 5 positive adjectives, 5 negative adjectives, and 5 catch-trials. Trait adjectives were randomly selected without replacement from 20 total traits. The catch-trials consisted of a black screen that was presented for the same length of time as the word trials and were included to increase jitter. Overall, subjects saw 40 adjectives for each of the 3 types of judgments (i.e., self, general, letter). Data Acquisition: High-resolution T1-weighted anatomical images were acquired using a Siemens Allegra 3.0T scanner using a single-channel head coil. Preprocessing: All preprocessing and analyses were performed 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: ANCOVAs and regressions assessed group differences and relationships across the sample with self-perspective scores, respectively.
Results: Overall, the MDD group endorsed fewer traits (i.e., fewer yes responses for positive traits and fewer no responses for negative traits) than HCs. Ratings were distributed in the following order, from highest to lowest: (1) general traits in HCs (2) general traits in MDD (3) self-ratings in HCs (4) self-ratings in MDD. Ratings differed between the HC and MDD groups for both self and general traits, as well as within the HC and MDD groups between self and general traits. An analysis of response times

revealed that the MDD group was overall slower than the HC group. Response times were distributed in the following order, from fastest to slowest: (1) general ratings in HCs (2) self-ratings in HCs (3) general ratings in MDD (4) self-ratings in MDD. Response times differed between HC and the MDD groups for both self and general traits, as well as within the HC and MDD groups between self and general traits. Response times did not differ between the groups for either positive or negative words. Regarding neural responses to trait adjectives, the MDD group exhibited hyperactivity in the precuneus for all trait adjectives, and both groups showed greater activity in the dorsomedial prefrontal cortex and posterior cingulate cortex in response to negative trait words. The dimensional approach using self-perspective scores across the entire sample revealed that greater activity in the precuneus was associated with worse positive self-perceptions.
Conclusions: Our results depicted that adolescents with MDD demonstrated hyperactivity in the precuneus. This hyperactivity extended to the processing of all trait adjectives and not only the self-referential traits. Our dimensional analysis revealed that positive self-perception scores across the entire sample drove group differences in the precuneus. These results emphasize the importance of using both traditional categorical analyses along with dimensional analyses to enrich our understanding of the underlying neurobiology of psychiatric disorders.
Keywords: depression, adolescents, self-perception, precuneus.
Disclosure: Nothing to Disclose.

W34. Adiponectin Deficiency Impairs Fear Extinction and Reduces Dendritic Spine Plasticity of Dentate Gyrus Granule Neurons

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Background: Adiponectin, a hormone produced and secreted by adipocytes, exerts its diverse biological effects through two distinct adiponectin receptors, AdipoR1 and AdipoR2. AdipoR1 and AdipoR2 are highly expressed in the hippocampus, which is required for the formation of the associations between contextual stimuli and aversive events and is actively involved in extinction of contextual fear memory. However, it is unknown whether adiponectin regulates hippocampal function and memory processes. Here, we studied the effects of adiponectin on conditioned fear, including memory formation, retrieval/expression, and extinction; and morphological features and synaptic connectivity of hippocampal neurons.
Methods: By employing genetic and pharmacological approaches, we identified the role of adiponectin in regulating fear memory at the behavioral level. We next characterized adiponectin action on the morphological and electrophysiological properties of granule neurons in the dentate gyrus, the hippocampal subfield acting as the gate of the hippocampal formation, to explore the mechanisms that mediate adiponectin effects.
Results: Adiponectin deficiency in mice resulted in deficit in contextual fear extinction, but acquisition and retrieval of fear memory were not affected. The dentate gyrus of the hippocampus has been suggested to mediate the formation of contextual representations of the spatial environment. Therefore, we analyzed the morphological and electrophysiological properties of dentate gyrus granule neurons in adiponectin-deficient mice. Dendritic length, dendritic arborization and spine formation of granule neurons were reduced in adiponectin-deficient mice. Furthermore, electrophysiological recording from adult hippocampal slices revealed that adiponectin deficiency decreased miniature EPSC (miniEPSC) frequency in dentate gyrus neurons in the presence of the sodium channel blocker TTX, suggesting decreased number of spines and functional synapses.
Conclusions: These results suggest that adiponectin is involved in contextual modulation of fear extinction, and its action on hippocampal neurons is required for excitatory synaptic connectivity of dentate gyrus neurons. These findings suggest a novel role of adiponectin in fear memory processing, and dendritic spine morphology and synaptic connectivity of dentate gyrus neurons.
Keywords: PTSD, Adiponectin, dentate gyrus, dendritic remodeling.
Disclosure: Nothing to Disclose.

W35. The Impact of Antipsychotic Medications on Sleep-dependent Consolidation of Motor Procedural Memory in Subjects with Bipolar I Disorder

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Background: Patients with schizophrenia show dramatic reductions of sleep-dependent memory consolidation, but it is not known whether this impairment also exists in patients with bipolar disorder. Cognitive impairment and deficits in functioning are common in bipolar individuals, even when euthymic, but it is not known whether procedural learning and its sleep-dependent consolidation are part of this impairment and whether the use of atypical antipsychotic medications might contribute to this.
Methods: To examine the effect of atypical antipsychotic medication on sleep-dependent consolidation of motor procedural memory, 31 euthymic outpatients with bipolar I disorder, divided based on whether they were treated with antipsychotic medication ($n = 14$) or not treated with antipsychotic medications ($n = 17$), were trained on a finger-tapping motor sequence task (MST) and tested on the following day. Overnight changes in MST performance were examined in each group and the difference in memory consolidation between groups compared.
Results: Euthymic subjects with bipolar I disorder treated with antipsychotic medications did not show significant improvement in motor procedural performance overnight (mean 5.4% ± sem 4.3; $p = 0.37$). Subjects not treated with antipsychotic medications had robust improvement in memory consolidation (mean 17.2% ± sem 4.3%; $p = 0.011$).

The groups did not differ significantly, however, in percent overnight improvement ($p = 0.11$). Antipsychotic treated subjects had slower motor speed overall, but this difference was also not significant. Controlling for baseline clinical and demographic characteristics did significantly change the results.
Conclusions: This study suggests that sleep-dependent memory consolidation of motor procedural memory is unimpaired in subjects with bipolar I disorder who are not prescribed antipsychotic medications, but may be impaired in bipolar I subjects who are prescribed these medications. It is not known whether antipsychotic medication causes this impairment or whether it is due to a factor inherent in bipolar I disorder in patients who require treatment with antipsychotic medication.
Keywords: Bipolar disorder, Sleep, Learning, Cognition.
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W36. Neuroimaging Social Behavior in Anorexia Nervosa

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Background: Responding to kindness is essential for human relationships. Problems with social relationships contribute to illness in anorexia nervosa, a psychiatric disease characterized by severe weight loss in pursuit of a socially-endorsed "thin ideal". Neuroeconomic games allow assessment of the neural responses during a simulated relationship, including moments of both positive and negative interactions. We examined how processing dynamic social interactions, both positive and negative, related to recovery from anorexia using a neuroeconomic game.
Methods: We compared three groups of subjects: healthy controls (HC, $n = 21$), subjects currently with anorexia nervosa (AN-C, $n = 23$), and subjects with long-term weight recovery from anorexia (AN-WR, $n = 19$). The AN-C subjects had all met full criteria for the illness during the 12 months before the MRI scan. The AN-WR subjects had met full criteria for anorexia previously, but had maintained a healthy weight with a body mass index greater than 19.0 for at least 2 years. In the office, subjects completed an attributional questionnaire, and clinician-measured assessments for depression, anxiety, and eating disorder behaviors. In a 3T scanner, the subjects played an interactive neuroeconomic game, the multi-round trust game, as trustee, with a computer-simulated healthy investor as their partner. Neural responses were examined when viewing the current investment of the partner. These responses were sorted based on reciprocity, a measure of change in the relationship. Reciprocity was further sorted into positive and negative rounds relative to whether the investor was behaving more positively or negatively toward the trustee. Whole-brain ANOVAs in SPM8 were used to identify group differences; whole-brain regressions examined relationships with the clinical and psychological measures.
Results: Neural responses to positive reciprocity, a signal of an improving relationship, were diminished in social cognitive regions, including the precuneus, temporoparietal junction, and fusiform gyrus in both the currently-ill and weight-recovered subjects with anorexia, but neural responses to negative reciprocity, a signal of a deteriorating relationship, were diminished only in the currently-ill participants in the fusiform. Furthermore, the positive personalizing bias, a measure of how strongly one believes that kindness comes from others rather than the situation, was inversely associated with neural activity throughout many social cognitive regions, including the bilateral temporoparietal junctions, the precuneus, fusiform gyri and the dorsal anterior cingulate.
Conclusions: Problems in perceiving kindness may contribute to the development of anorexia, but recognizing meanness may be a significant cognitive shift relevant to recovery from anorexia. The positive personalizing bias provides a pen and paper assessment of neural activation in response to kindness. In future studies, determining whether changes in positive personalizing bias are related both to specific therapeutic treatments as well as neural responses could provide a clear target for cognitive treatment of social components in anorexia nervosa.
Keywords: social cognition, eating disorders, attribution, neuroeconomic.
Disclosure: Nothing to Disclose.

W37. Genetic Influence of Kcnn3 on Extinction Learning Identifies a Novel Target for Enhancing Inhibitory Learning of Alcohol-associated Cues

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Background: Exposure to alcohol-related cues contributes to high rates of relapse in treatment-seeking alcoholics. The ability to facilitate the extinction of alcohol-associated cues using cognitive enhancers is a promising therapeutic approach to reduce relapse rates. Small-conductance calcium-activated potassium (KCa2) channels have been implicated in synaptic plasticity, cognition, and addiction, and modulating these channels can enhance the extinction learning of food-seeking and fear behaviors. Recent evidence has also demonstrated that genetic factors can influence extinction learning in mice. However, the specific genes that regulate extinction learning have not been identified, and it is currently unknown if modulating KCa2 channels can facilitate extinction of alcohol-associated memories. Thus, the purpose of this study was to determine if the genes that encode KCa2 channels (Kcnn1-3)

predict extinction learning in BXD recombinant inbred (RI) strains of mice and if blocking KCa2 channels enhances extinction learning of alcohol cues.
Methods: The present study employed an integrative functional genomics approach using databases in GeneNetwork. Correlations were calculated between Kcnn1-3 transcript levels in the prefrontal cortex and the number of trials to extinguish responding for food-related cues in ethanol-naïve BXD RI strains of mice. To complement the genetic findings, we examined the ability of apamin, a KCa2 channel allosteric inhibitor, to facilitate extinction learning and attenuate spontaneous recovery of alcohol-seeking behavior. Wistar rats were trained to self-administer 10% EtOH and then exposed to extinction training. Vehicle or apamin was administered 5 min prior to each extinction session. Once the rats reached extinction criteria, they remained in their home cages for 3 weeks prior to testing on a single 30 min spontaneous recovery session.
Results: Preliminary evidence showed that only Kcnn3 transcript levels in the prefrontal cortex (PFC) of BXD RI strains of mice were significantly correlated with the number of trials to extinguish responding for food-related cues ($R2 = 0.607$, $p = 0.0389$ $n = 7$ strains). We found that lower transcript levels of Kcnn3 in the PFC were associated with facilitated extinction behavior (i.e., enhanced learning). Apamin administration prior to each extinction session significantly enhanced the extinction of alcohol-seeking behavior in Wistar rats [$F(13,273) = 4.8$, $p < 0.001$; $n = 12$ control; $n = 11$ apamin]. This was evidenced by significantly reduced responding on multiple days of extinction (p values < 0.05) and fewer sessions required to reach extinction criteria [$t(21) = 5.1$, $p < 0.0001$]. Rats treated with apamin prior to the extinction session also responded significantly fewer times on the previously active lever during the spontaneous recovery test session [$t(10) = 4.5$, $p = 0.001$; $n = 6$].
Conclusions: These data indicate that PFC Kcnn3 transcript levels influence extinction learning in ethanol-naïve BXD RI mice. Consistent with our genetic findings, modulation of KCa2 channels with apamin facilitates extinction learning and attenuates spontaneous recovery of alcohol-seeking behavior in Wistar rats. Thus, KCa2 channels may be a novel pharmacogenetic target for enhancing cue exposure therapy in the treatment of alcohol use disorders. The authors acknowledge the support of NIH grants AA020930 and AA020537.
Keywords: Alcoholism, KCa2 channels, Extinction learning, genetics.
Disclosure: Nothing to Disclose.

W38. Heightened Negative Emotionality Underlies Affective Hyper-reactivity and More Pronounced Drug-seeking in Cocaine Users with High Trait Anger

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Background: The combination of cocaine use and chronic anger traits is an important public health concern, since individual differences in negative emotion can contribute both to the cycle of drug addiction and to the cycle of violence. Just as drug addiction is characterized by excessive salience attribution to drugs and related cues, anger prone individuals also have excessive reactivity toward provocative cues. Although abnormally high trait anger and poor anger control are dominant features in drug addiction, their role in motivated attention to salient cues in addiction is not well understood. Therefore, in this study we used event-related potentials (ERPs), objective markers of motivated attention, to study responsiveness to salient cues in individuals with cocaine use disorder (CUD) with and without high anger; we further ascertained association between these brain responses and personality traits related to negative emotionality. We hypothesized that CUD who also endorse excessive anger traits will be especially hyper-reactive to emotionally charged stimuli.
Methods: Forty male CUD participated in the study. Participants were classified as High Anger (CUD-HA, $N = 10$) based on the State-Trait Anger Expression Inventory-2 (STAXI-2) age-normed mean scores of 75%tile or above for trait anger and of at 25%tile or below for anger control. Low Anger (CUD-LA, $N = 14$) were defined as individuals with age-normed mean scores of 50%tile or below for trait anger and of 50%tile or above for anger control (16 participants with intermediary scores were excluded from these analyses). Both groups were matched on age, race, verbal and non-verbal IQ, and education. Participants also completed the Multidimensional Personality Questionnaire (MPQ) for assessment of trait negative emotionality and the Craving Questionnaire (CQ) for assessing drug-seeking. ERPs were acquired while participants passively viewed pleasant, unpleasant, neutral, and cocaine-related pictures. The late positive potential (LPP) component of the ERP was scored to index motivated attention to these stimuli. The LPP response to each emotionally salient picture was normalized to each individual's LPP response to neutral pictures.
Results: A 3 (picture-type: pleasant, unpleasant, and cocaine-related) $\times$ 2 (groups: CUD-HA and CUD-LA) mixed ANOVA revealed a significant group main effect [$F(1,22) = 7.67$, $p = 0.011$], such that compared to CUD-LA, CUD-HA had higher LPPs to all emotional pictures [driven by responses to both unpleasant ($t(22) = 2.45$, $p = 0.023$) and cocaine-related ($t(22) = 2.19$, $p = 0.040$) but not to pleasant pictures, $p = 0.119$]. The picture-type main effect and picture-type $\times$ groups interaction did not reach significance ($p > 0.26$). Similarly, CUD-HA scored higher than CUD-LA on MPQ's higher order negative emotionality composite score ($t(22) = 7.63$, $p < 0.001$) driven by the traits such as stress reaction ($t(22) = 3.19$, $p = 0.006$), alienation ($t(22) = 4.50$, $p < 0.001$), and aggression ($t(22) = 4.12$, $p = 0.001$); there were no group differences in positive emotionality-related traits ($p > 0.129$). Compared to CUD-LA, CUD-HA also scored higher on craving ($t(22) = 3.66$, $p = 0.003$) on the day of the ERP study. Moreover, the higher order negative emotionality composite score was correlated with LPPs to both unpleasant ($r = 0.51$, $p = 0.012$) and cocaine-related ($r = 0.45$, $p = 0.026$) pictures across both groups. Lastly, the desire of cocaine in last 24 hours, ascertained via CQ, was correlated with the negative

emotionality composite score ($r = 0.68$, $p < 0.001$) and LPPs to cocaine-related pictures ($r = 0.48$, $p = 0.018$).
Conclusions: Individuals with CUD and abnormally increased trait anger endorsed higher self-reported trait negative emotionality, increased drug desire, and higher electrocortical reactivity to emotional (cocaine and unpleasant) pictures. The same direct associations (between trait negative emotionality, acute desire for cocaine, and electrocortical reactivity to emotional pictures) were observed across the groups in correlation analyses. Interestingly, the two groups did not differ in trait positive emotionality or LPP response to pleasant pictures, supporting prior reports of unique involvement of negative (but not positive) emotionality in characterization of high trait anger. Thus, these results extend a previously established affective profile (negative > positive) to high trait anger in the context of drug addiction. Overall, these results highlight the interplay between increased negative emotionality and affective hyper-reactivity in addicted individuals with higher anger traits, which may significantly contribute to the course and severity of drug addiction.
Keywords: addiction, anger, negative emotionality, ERP.
Disclosure: Nothing to Disclose.

W39. Abnormal Social Cognition Among Veterans at High Risk for Suicide

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Background: Intact social cognitive skills are crucial for developing and maintaining social relationships. Decreased social support and low sense of belonging (termed "thwarted belongingness") are known risk factors for suicide. Borderline personality disorder (BPD) severely impairs social functioning and has a high - about 10% - lifetime risk for suicide. Growing evidence suggests that BPD patients have social cognitive impairments, such as abnormal emotion recognition and understanding of mental states (mentalizing). However, the impact of social cognitive abnormalities on suicidal behavior remains largely unexplored. In this study, we aimed to examine the relationship between social cognition, BPD diagnosis and suicide risk using two objective, validated behavioral paradigms to measure social cognition.
Methods: Subjects: 68 male and female veterans (41 fulfilling DSM criteria for BPD, and 27 without BPD) were recruited from an outpatient mental health clinic at a VA medical center. They were classified into 2 groups: a "high risk group", including those with a history of one or more suicide attempts, or at least one psychiatric hospitalization due to serious suicidal ideation; and a "low risk group", including those with no history of suicide attempts or suicidal ideation. Measures: We examined social cognition abnormalities using two objective, validated behavioral paradigms –the Reading of the Mind in the Eyes Test (RMET) - and the Movie for the Assessment of Social Cognition (MASC)-. The RMET is an established social cognition task requiring emotion recognition by focusing only in the facial eye region. The MASC is a real-life, naturalistic social cognition task, that measures subtle mentalizing difficulties, with high inter-rater reliability (ICC = 0.99), test-retest reliability ($r = 0.97$), and internal consistency (Cronbach's $\alpha = 0.86$). It involves watching a 15 min movie about 4 characters. Multiple-choice questions about the characters' feelings/thoughts/intentions are asked, yielding quantitative (mentalizing accuracy) and qualitative measures (hypomentalizing/hypermentalizing errors). Performance on the social cognition outcome measures (RMET and MASC) was compared across groups (high-risk vs low-risk) and diagnoses (BPD vs no BPD) using ANOVA.
Results: Mentalizing scores on the MASC hypomentalizing subscale were significantly more impaired among those in the high-risk group for suicide, approximately 80% of whom fulfilled criteria for BPD ($F = 4.7$;$df = 1$;$p = 0.033$). RMET scores did not differ between the "high-risk" and the "low-risk" groups, or between those with or without BPD. Due to the very low number of patients in the high-risk group who did not fulfill criteria for BPD ($n = 10$) and the very low number of BPD patients in the low-risk group ($n = 3$), we could not test interaction effects between group (high vs low-risk) and diagnosis (BPD vs no BPD).
Conclusions: Our results suggest a potential association between impaired social cognition and a higher risk for suicide. Because intact social cognition is required to develop and maintain social relationships, the effect of poor social cognition on suicide may be mediated by a decrease in social support and social belongingness. Future studies should analyze the effect of impaired social cognition on social support and perceived social belongingness. Because of the limited sample size, our results should be interpreted as exploratory and hypothesis-generating.
Keywords: Mentalizing, Social Cognition, Suicide, Borderline Personality Disorder.
Disclosure: Nothing to Disclose.

W40. D-Cycloserine Enhances Synaptic Plasticity and Cortico-Striatal Dependent Learning in Healthy Volunteers

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Background: The N-methyl-D-aspartate receptor (NMDAR) is a primary excitatory glutamate receptor. It plays a key role in synaptic plasticity, including long-term potentiation (LTP), learning, and memory consolidation in the mammalian brain. Given the role of NMDARs in synaptic plasticity and learning, interest has grown in NMDAR-agonists as potential cognitive enhancers. Whereas enhancing NMDAR function via direct stimulation of the glutamate site can increase the risk of excitotoxicity, indirect stimulation via the glycine site offers a safer mode to facilitate receptor activity. D-cycloserine (DCS) is a partial agonist at the glycine-binding site and readily crosses the blood-brain barrier, is approved by the FDA for daily use as an anti-

tuberculosis drug, and has few side effects at low doses. While DCS when administered in conjunction with exposure therapy for anxiety enhances the effect of training, studies of the effects of DCS on various cognitive performance deficits in patient groups and on cognition in healthy participants have yielded mixed results. Differences in dose, administration schedule, or study population may provide some explanation for the mixed findings; however, an important consideration may be that effects of DCS are best seen under task and intervention conditions that depend on long-term potentiation and provide opportunity for learning and/or memory consolidation. This idea has yet to be tested systematically in any published human study. To begin clarifying the conditions and mechanisms by which DCS enhances cognition, we therefore conducted a double-blind, randomized DCS versus placebo study to test the hypotheses that: 1) DCS preferentially enhances performance on tasks with greater opportunity for learning and memory consolidation compared to tasks that minimize these effects; 2) DCS enhances LTP; and 3) increased LTP predicts improved learning on cognitive tasks.

Methods: Sixty-three healthy college students were enrolled in the study and underwent testing on two consecutive days. On the first day of testing, participants were randomized to receive either DCS (n = 31) or placebo (n = 32). Participants and then completed a visual LTP task while undergoing EEG. Visual evoked potentials (VEPs) in response to a black and white checkerboard stimulus were assessed in 2 minute blocks before and after exposure to a tetanizing high frequency stimulus (HFS). Participants subsequently completed three cognitive tasks: the weather prediction task (WPT), an information integration (II) learning task, and a spatial n-back task in random order. The WPT and II tasks are cortical-striatal dependent implicit, probability learning tasks that require repeated practice with stimuli and feedback in order to reach optimal performance. The n-back task assesses working memory. Of note, to facilitate comparison of the effects of DCS on a task with greater opportunity for learning and memory (i.e. the II task) to a task that minimized these effects (i.e. the n-back task), the stimuli, trial structure, and auditory feedback in the II and n-back tasks were designed to be identical such that the only difference subjects experienced while completing these two tasks was what they were asked do with the stimuli. On the second day of testing, participants repeated testing on the three cognitive tasks without drug administration.

Results: On the LTP task, DCS enhanced potentiation of the VEP following HFS, as evidenced by increased N1-P2 peak to peak amplitude across 4 post-HFS blocks in participants who received DCS compared to those to who received placebo. DCS also enhanced performance on the WPT and II task, as evidenced by improved performance in the DCS group compared to the placebo group across testing days for the WPT task and during early learning trials for the II task. Conversely, on the spatial n-back task there was no effect of DCS despite identical stimuli, task structure, and auditory feedback during the n-back and II tasks. Finally, greater potentiation of the VEP during early post-HFS blocks significantly predicted improved early learning on the II task across groups.

Conclusions: These results support the hypotheses that DCS enhances LTP and preferentially enhances performance on tasks requiring learning for optimal performance. Results also suggest that the differential effects of DCS on learning tasks compared to working memory tasks may be mediated by the effects of DCS on LTP. These results support a role for the NMDAR in cortical-striatal dependent learning. Overall, these results highlight the importance of considering mechanisms of action when studying the effects of NMDAR-agonists on various cognitive domains and suggest that targeting cognitive domains consistent with mechanistic-driven hypotheses may yield more fruitful results when using NMDAR-agonists as cognitive enhancers.

Keywords: d-cycloserine, NMDA receptor, long-term potentiation, learning.

Disclosure: Nothing to Disclose.

W41. Cognitive Dysfunction in Combat Veterans is Related to Attenuated Dorsal ACC Activation During Interference Processing

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Background: The multi-source interference task (MSIT) was developed as a neural and behavioral assessment of dorsal prefrontal function, and has shown to be particularly sensitive to dorsal anterior cingulate cortex (dACC) activation (Bush and Shin, 2006). PTSD has been associated with dACC dysfunction across numerous studies, particularly during interference or other executive function related tasks. However, some studies have reported exaggerated activation while others have reported attenuated activation (i.e., Moores et al., 2008; Shin et al., 2011). There has also been little research investigating whether dACC activation during interference-related paradigms relates to the more general neuropsychological disturbances often identified in PTSD. The current study used an a priori anatomical region of interest (ROI) approach, which may be more generalizable than voxel-based approaches, to investigate dACC function for combat veterans. In addition, we examined the relationship between dACC ROI activation and both PTSD symptoms and neuropsychological function.

Methods: As part of an ongoing study, 27 male combat veterans who served in recent conflicts in Iraq or Afghanistan (mean age = 33.0, SD = 6.20, all male veterans) completed a modified version of the MSIT task (Bush et al., 2003) concurrently with functional magnetic resonance imaging (fMRI). This task is presented as a block design and requires subjects to identify the digit that is unique amongst a series of three. On the congruent trials, one number is presented in its sequentially congruent location along with two Xs (i.e., X2X). For the incongruent trials, the unique number is presented in an incongruent location along with two other numbers (i.e., 211). In the current study, the size of the digits was used as an additional source of interference, thus increasing the difficulty level of the task (Matthews et al., 2007). We extracted average percent signal change (PSC; Incongruent – Congruent trials) from anatomical ROIs within the cingulate, including the ventral ACC, dACC, and mid cingulate cortex. The clinician administered PTSD scale (CAPS) was administered to diagnose PTSD and to quantify symptom severity. A battery

of validated neuropsychological measures was administered, including measures of executive functioning, speed of information processing, attention and working memory, and verbal memory. Raw scores were converted into z scores for each task based upon previously published normative data. These scores were then averaged to obtain a single measure of neuropsychological function. Independent samples t-tests were used to compare PTSD and control groups in regards to ROI PSC and neuropsychological performance. Spearman's rho correlations were used to investigate the relationship between ROI PSC, CAPS total severity score, and neuropsychological performance.

Results: The PTSD group demonstrated attenuated dACC activation for the MSIT (Incongruent-Congruent) but no differences in vACC or MCC PSC. Moreover, the groups did not differ on neuropsychological performance. For the combat veteran group as a whole, as well as within the PTSD group, those veterans with greater dACC activation also showed better neuropsychological performance. These results remained significant when correcting for multiple comparisons. Regression analyses indicated that, within the PTSD group, dACC PSC accounted for 54% of the variance in neuropsychological performance. Dorsal ACC activation was not significantly related to years of education and estimated full scale IQ. At time of presentation, these results will be updated after inclusion of additional subjects and supplementary analyses of individual neuropsychological assessment scores.

Conclusions: The current results demonstrate that dACC dysfunction can be detected in PTSD using an anatomical ROI approach with the MSIT. In addition, activation levels within the dACC may be clinically significant in relation to overall cognitive function in combat veterans, and PTSD patients specifically. Interestingly, the directionality of findings in the dACC is inconsistent with some previous studies using the MSIT. This inconsistency is a notable characteristic of the literature related to dACC activation and executive function in PTSD. Future investigations will need to determine whether this inconsistency is due to the specific population studied, time since traumatic event, or a result of different dACC subregions that contribute to executive functions such as interference or inhibition. Regardless of the inconsistencies in the literature, the current results support the robustness of dACC dysfunction in PTSD as measured by the MSIT and indicate that this may be a mechanism contributing to PTSD-related cognitive difficulties.

Keywords: trauma, PTSD, anterior cingulate cortex, cognitive.

Disclosure: Nothing to Disclose.

W42. Behavioral and Neural Stability of Attention Bias to Threat in Healthy Adolescents

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Background: The preferential allocation of attention to threats is a hallmark of anxiety disorders (Bar-Haim et al., 2007). This attention bias has important implications for treatment. For example, experimental work demonstrates that an individual's attention bias to threat is malleable: a reduction in threat bias is linked to reduced anxiety vulnerability (Beard, 2011; Hakamata et al., 2010). However, prior studies find that attention bias is not stable across time, which complicates attempts to target this marker in treatment. This lack of stability may be because prior studies base estimates of stability of bias across time only on behavior (Britton et al., 2013). The current study uses functional magnetic resonance imaging (fMRI) to measure the stability of attention bias in adolescents.

Methods: The current study included 36 typically developing youth (M = 13.39 yrs, SD = 2.31 yrs). The dot-probe task was used to assess attention bias to threat. In the dot-probe task, participants were asked to perform a simple probe discrimination task. Prior to the onset of the probe, two faces appeared on the screen displaying either a threatening or neutral expression. Following the face display, the probe appeared in the same location as one of the previously viewed faces. The task consisted of three different trials types: congruent trials in which the probe appeared behind the threatening face, incongruent trials in which the probe appeared behind the neutral face; and neutral-neutral trials as a control condition. Children completed the dot-probe task at two time points during fMRI data acquisition. The average time interval between assessments was 9.23 weeks (SD = 2.31 weeks). In the current study, attention bias to threat was examined by comparing behavioral and neural response to incongruent vs. congruent trials. In addition, the differences between any threat trial (collapsing across congruency) vs. neutral trials were compared. For the behavioral analyses, reaction time based attention bias scores at the two visits were tested for significant correlations. For the fMRI analyses, intra-class correlation (ICC) was used to examine the stability of neural activity associated with attention bias to threat. Clusters surpassing an ICC $\geq$ .50 and k $\geq$ 20 voxels were considered significant. Correlations analyses were used to examine relations between behavioral and neural measures of attention bias at each time point. Additionally, the temporal correlations of child and maternal reports of anxiety were examined.

Results: The behavioral analyses revealed no significant correlations between the two time points for either the incongruent vs congruent bias ($r(35) = .04$, $p = .84$), or the angry vs. neutral bias ($r(35) = -.28$, $p = .10$). The imaging stability ICC analyses revealed several areas that demonstrated stable activation across time. Activation within the vlPFC [left: 18.8, −18.8, −8.8, 115 voxels, ICC = .70; right: −36.2, −36.2, 6.2, 32 voxels, ICC = .77] and striatum [-6.2, −6.2, −1.2; 115 voxels; ICC = .80] were consistent across time for the incongruent vs. congruent contrast. In regards to the contrast of all angry trials vs. neutral trials, two areas of activation in the vmPFC [-48.8 -8.8. -16.2, 83 voxels, ICC = .72; -38 −43.8 −6.2, 26 voxels, ICC = .70] and temporal pole [31.2, −18.8. −23.8; 33 voxels, ICC = .70] showed consistent activation patterns across time. Correlation analyses revealed no statistically significant relations between behavioral and neural measures on the incongruent vs. congruent trials (Time 1: all $rs < |.20|$, $ps > .24$; Time 2: all $rs < |.28|$, $ps > .1$) or on the angry vs. neutral trials (Time 1:

all rs<|.28|, ps>.11; Time 2: all rs<|.29|, ps>.09). The results did reveal significant correlations across time between parent (r = .75, p < .01) and child-reported anxiety, (r = .85, p < .01).

Conclusions: Consistent with prior work (Britton et al., 2013), the current findings provide evidence of stable neural correlates associated with attention bias to threat in a group of healthy youth. Specifically, activation differences in the vlPFC and striatum on incongruent compared to congruent threat trials were highly stable across time. Temporal pole and vmPFC activation in response to all angry trials compared to neutral trials were also consistent across time. Despite the neural stability, the behavioral measures of attention bias to threat were not reliable across time. Reliability of measures based on reaction time difference scores can be difficult to detect (Salthouse & Hedden, 2002), but the current findings suggest that a child's neural response to threat on the dot-probe task offers a robust index of attention bias to threat. As such, future work examining attention bias in anxious youth may be bolstered by the use of neuroimaging techniques. Additionally, the current findings highlight several important brain regions associated with stable attention bias that may inform target brain regions for future bias-focused treatment research.

Keywords: Attention, fMRI, Information-Processing Biases, Adolescents.

Disclosure: Nothing to Disclose.

W43. Hippocampal Subfield Volume Abnormalities in Individuals with Schizophrenia

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Background: Individuals with schizophrenia show robust episodic memory and hippocampal volume deficits though regional abnormalities within the hippocampal formation remain largely unknown. This study examines regional hippocampal volume abnormalities and their relationship with episodic memory performance in a large cohort of individuals with schizophrenia compared to healthy volunteers who participated in the Function Biomedical Informatics Research Network Phase 3 study.

Methods: We assessed hippocampal total, hippocampal subregion [Cornu Amonis (CA) 1, CA2-3, CA4-Dentate Gyrus (DG), Subiculum, Pre-Subiculum, Fimbria, Hippocampal Fissure, and Posterior Hippocampus], and intracranial volumes with FreeSurfer 5.1.0, from high-resolution structural magnetic resonance imaging (MRI) brain scans, in 166 adults with schizophrenia and 163 demographically similar healthy volunteers. Additionally, we examined correlations between hippocampal subfield volumes and verbal episodic memory.

Results: Individuals with schizophrenia had significantly smaller presubiculum, subiculum, CA4-DG, CA2-3, and fimbria volumes, but not CA1, posterior hippocampus, and hippocampal fissure volumes. Among controls, left hippocampal volumes and among patients left CA4-DG and CA2-3 showed significant positive correlations with total correct on a verbal list-learning task.

Conclusions: The volumetric findings support hippocampus models of psychosis that posit abnormalities in the presubiculum, subiculum, Cornu Ammonis (CA) regions 2-4, and the dentate gyrus. They do not support models that posit a primary deficit in CA1, a region previously associated with higher CA1 cerebral blood volume (CBV) using Gadolinium-enhanced resting-state imaging in individuals with or at risk for psychosis. This study provides neuroimaging-based evidence for an association between episodic memory performance and dentate gyrus and CA2-3 volume deficits in schizophrenia. These findings suggest a unique role for the CA4-DG and CA2-3 regions in episodic memory deficits in schizophrenia.

Keywords: schizophrenia, psychosis, hippocampus, dentate.

Disclosure: Dr. Van Erp consulted for Roche Pharmaceuticals. Dr. Bustillo consulted with Novartis and Otsuka Pharmaceuticals. Dr. Mathalon is a consultant for Bristol-Myers Squibb and consulted for Roche Pharmaceuticals. Dr. Preda consulted for Boehringer-Ingelheim. Dr. Potkin has financial interests in Bristol-Myers Squibb, Eisai, Inc., Eli Lilly, Forest Laboratories, Genentech, Janssen Pharmaceutical, Lundbeck, Merck, Novartis, Organon, Pfizer, Roche, Sunovion, Takeda Pharmaceutical, Vanda Pharmaceutical, Novartis, Lundbeck, Merck, Sunovion and has received grant funding from Amgen, Baxter, Bristol-Myers Squibb, Cephalon, Inc., Eli Lilly, Forest Laboratories, Genentech, Janssen Pharmaceutical, Merck, Otsuka, Pfizer, Roche, Sunovion, Takeda Pharmaceutical, Vanda Pharmaceutical, NIAAA, NIBIB, NIH/NCRR, University of Southern California, UCSF, UCSD, Baylor College of Medicine. The remaining authors declare no potential conflict of interest.

W44. Effects of Alcohol on Encoding and Consolidation of Memory for Affective and Alcohol-related Stimuli

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Background: Alcohol is known to affect memory in ways that could affect alcohol abuse. Here we examined memory accuracy following alcohol administered either before (encoding) or immediately after (consolidation) viewing affective and alcohol-related stimuli. We hypothesized that alcohol would impair memory at encoding and enhance memory during consolidation, and that these effects would differ according to stimulus type.

Methods: Healthy social drinkers attended a viewing session in which they received alcohol (0.8 g/kg) or placebo before or immediately after viewing affective and alcohol-related images. Exactly 48 hours later they attended a retrieval session during which they were asked to recall and recognize the stimuli in a surprise memory test in a drug-free state. Subjects were randomly assigned to one of three conditions: Encoding (N = 20), Consolidation (N = 20), or Control (N = 19). The Encoding group received alcohol before viewing the images, and placebo immediately after. The Consolidation group received placebo before viewing

the images, and alcohol immediately after. The Control group received placebo before and after.
Results: In the Encoding condition alcohol impaired recollection and recognition memory (ps < .03). It impaired recollection for all stimulus categories except alcohol-related (ps < .03), and it impaired recognition for negative stimuli only (p = .02). By contrast, in the Consolidation condition, alcohol enhanced recognition memory (p = .01), specifically for alcohol-related (p < .01), positive (p = .02), and neutral stimuli (p = .03).
Conclusions: As hypothesized, alcohol impaired memory when administered prior to encoding, but enhanced memory when administered during initial consolidation. Further, these effects differed according to stimulus category: alcohol preferentially impaired memory for negative stimuli and enhanced memory for positive and alcohol-related stimuli. Such effects could increase positive memory biases for drinking episodes, as well as enhance learning for stimuli associated with drinking, potentially increasing the propensity to initiate future drinking episodes.
Keywords: alcohol, memory, encoding, consolidation.
Disclosure: Nothing to Disclose.

W45. Behavioral and Cognitive Constructs Underlying Disorders of Disinhibition

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Background: The discovery of clinical observation and biomarker tests that complement and enhance diagnostic categories has the potential to improve our understanding of the underlying biological mechanisms of psychiatric conditions thereby accelerating targeted treatment development. For example, overlapping neural circuitry and abnormalities in dopaminergic neurotransmission may produce similar patterns of disinhibited behavior in patients with diverse diagnoses, including bipolar disorder (BD) and substance use disorders. This tenet underlies the National institute of Mental Health (NIMH) Research Domain Criteria (RDoC) approach that emphasizes the discovery and characterization of basic dimensions of functioning studied across multiple units of analysis independent of traditionally defined disorders. Disinhibition can be understood as a state of reduced control over one's behavior, reflecting a subcomponent of cognitive control, and is a core feature of several psychiatric illnesses including BD and substance dependence. In fact, much of the morbidity associated with these conditions can be ascribed to disinhibition, which manifests as increased impulsivity, risk-taking behavior and suicidal gestures. This study aimed to identify basic dimensions of behavioral and cognitive functioning central to disinhibition across several diagnostic categories including inpatient and outpatient BD, past methamphetamine dependence and healthy individuals taking part in an amphetamine challenge study.
Methods: A total of 114 participants were included in this analysis: manic BD inpatients (n = 11); euthymic BD outpatients (n = 24); people with a history of methamphetamine dependence (n = 23); and healthy participants who received an amphetamine stimulant challenge (n = 48; 10 mg dose n = 15, 20 mg dose n = 16) placebo (n = 17) or no treatment (n = 8). Motor activity and cognitive functioning were evaluated using the human behavioral pattern monitor (hBPM) paradigm, the Iowa Gambling Task (IGT), and the Conners' Continuous Performance Task (CPT). The hBPM, a human version of the animal behavioral pattern monitor, is a room that contains several items of furniture (but no chairs) and a number of small colorful and tactile objects. The subjects were fitted with an ambulatory monitoring device and placed in this novel environment for 15 minutes without instruction while their activity was monitored by a digital video camera embedded in the ceiling. This paradigm has been used previously to identify a signature pattern of hyper-exploration in manic BD inpatients that persisted following treatment with antipsychotic and/or mood-stabilizing medication and was also evident in euthymic BD outpatients. Six items derived from the test scores were included in the Principal component analysis (PCA) with a varimax rotation (Kaiser normalization): mean acceleration over a 15 minute period; counts (the number of discrete instances of movement or the smallest measured change in x y coordinates, higher values suggest more motor activity) and total number of object interactions in the hBPM; IGT net gain; CPT d prime (d'; a measure of the individual's discriminative power); and CPT hit rate reaction time (average speed of correct responses during the entire test).
Results: The PCA identified three prominent and distinct factors. The behavioral measures with the highest loading for Factor 1 were acceleration (0.876), counts (0.871) and the total number of object interactions (0.534). Factor 1 may be consistent with the RDoC arousal construct in the arousal and regulatory systems domain. For Factor 2, CPT d' and CPT hit rate reaction time had the highest loading (0.855 and 0.874, respectively) and may correspond to the attention construct and possibly the response selection, inhibition or suppression subconstruct. High IGT net gain (0.916; indicative of less risk-taking) and weakly fewer total object interactions (− 0.479) had the highest loading for Factor 3 and appears to represent the approach motivation construct, specifically the action selection/preference-based decision making subconstruct in the positive valence systems domain.
Conclusions: In the course of our studies we were able to identify factors that relate to the NIMH RDoC constructs by assessing separate populations of subjects across a battery of inhibitory-associated tasks. Specifically, three distinct factors were identified that relate to the arousal, cognitive control and the positive valence constructs described in the RDoC initiative. Importantly, these factors did not simply represent diagnostic groups of subjects but reflected specific attributes of behavior observed across the population. These factors indicate an organizing principle underlying disorders of disinhibition. Hence, these factors may relate more to the direct biological substrate than traditional diagnostic categories, thus enabling the development of neural substrate-targeted therapeutics.
Keywords: disinhibition, bipolar disorder, motor activity, attention.
Disclosure: Nothing to Disclose.

W46. Oxytocin Modulates EEG and Pupillary Responses to Social Stimuli in Schizophrenia: A Pilot Within-Subject Double-blind Crossover Study

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Background: Oxytocin, a neuropeptide hormone, plays an important role in regulating human social behaviors. As a result, it has been explored as a potential therapeutic agent for psychiatric disorders that are associated with impairments in social behaviors including autism and schizophrenia. Although a substantial body of evidence indicates that intranasal administration of OXY has effects on social behaviors, there is a very limited understanding as to how OXY's effects on brain targets are linked to its behavioral effects. Examining neural target engagement of oxytocin on a variety of socially-relevant tasks would provide valuable information regarding the relation of neural responses to selected doses, its duration of effects, and its mechanism of action. The current study examined EEG and pupillometry responses to a variety of socially-relevant tasks after oxytocin or placebo was administered to patients with schizophrenia to examine brain-based biomarkers of target engagement by oxytocin.
Methods: Eleven male patients with stable schizophrenia participated in a double-blind, within-subjects cross-over experiment, with testing on separate days approximately 1 week apart. All participants were taking antipsychotic medication at the time of testing. Participants were randomly assigned (double-blind) to receive either oxytocin (OT) or placebo (PL), and one week later cross-over assignment was administered. OT nasal spray (50 IU/mL) and placebo intranasal spray were prepared in 12 mL multi-use bottles. A single dose of OT or PL was administered by instructing participants to spray four puffs into each nostril, for a total dose of 40 IU OT or PL thirty minutes prior to testing. Participants first had EEG recorded while viewing a series of movie clips depicting biological or non-biological motion. For EEG, we examined mu-suppression in the 8-13 Hz range. Next pupillometry was recorded in two separate tasks: 1) during viewing of emotional, non-emotional, and scrambled faces; and 2) during a modified biological motion task. We examined change in pupil size from a 100 ms baseline between 800-3000 ms post-stimulus onset. The EEG and pupillometry biomarkers were evaluated while blind to study condition.
Results: For EEG, greater mu-suppression was seen after administration of OT vs. PL, with an effect size of $d = 0.24$. For pupillometry, we saw a complex pattern of results. In the biological motion task, pupil dilation was greater on OT vs. PL ($p < 0.05$), regardless whether the stimulus was classified as biological or not. In the facial affect processing task, pupil dilation was smaller on OT vs. PL to fearful faces only.
Conclusions: The results of the current study highlight the ability of OT to directly affect the brain's ability to process social information. While this initial pilot study had a small n, the results clearly demonstrate target engagement of OT. Mu suppression in the 8-13 Hz range (a neural measure of the brain's response reflecting greater allocation of cortical resources to social stimuli) was greater after administration of OT compared to PL. OT has been shown to decrease fMRI activation of the amygdala when viewing fearful faces. Decreased pupil dilation to fearful faces after OT administration may indirectly reflect decreased amygdala activation to negatively-valenced stimuli. The initial results of this pilot study demonstrate that target engagement of OT can be assessed with brain-based biomarkers and support further investigation of OT in clinical trials in disorders that affect social behavior.
Keywords: oxytocin, schizophrenia, EEG, pupillometry.
Disclosure: Nothing to Disclose.

W47. Human Superior Temporal Sulcus Subserves both Concrete and Abstract Social Cognition in Typical Development

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Background: Lesion, electrophysiological and imaging studies in humans and non-human primates implicate the right superior temporal sulcus (STS) in mediating visuospatial awareness (Karnath 2001) and visual social information processing (Haxby et al. 2000). Millisecond-resolved STS oscillatory signals are implicated in decoding the emotional meaning of dynamic facial cues (Jabbi et al. 2014), and dysfunctions of the STS are associated with social cognitive deficits in autism, fragile X syndrome, and schizophrenia. Although the ability to decipher concrete social signals is shown to predict more complex social cognitive skills such as understanding other people's mental states and intentions and adapting accordingly during social interactions (Ihnen et al. 1998), a convergent neural mechanism linking concrete and abstract social cognitive processes has not been identified. Here, we hypothesized that the magnitude of right STS responsiveness to concrete dynamic emotional cues would predict the neural network underpinnings of abstract social cognition.
Methods: Participants: Eighteen typically developing children, ages 5-17 years (mean age = 14.35 years; nine females) participated in two fMRI experiments. In experiment1, videos displaying highly concrete depictions of disgusting, pleasant and emotionally neutral facial expressions of gustatory experiences (Jabbi et al. 2007) were presented in a randomized event-related design during fMRI. Participants were required to watch the videos. In experiment2, videos of highly abstract (Weisberg et al. 2012) social and non-social scenes (moving geometric shapes symbolizing social interactions or routine mechanical operations, respectively) were presented to the same participants in a randomized event-related design. For both experiments, participants responded to a post stimulus button prompt after each trial Statistical Analyses: After preprocessing (8mm smoothing) and normalization using statistical parametric mapping (SPM5), one-sample T contrasts were run in SPM5 at the first level to localize BOLD reactivity to observing a) facial expressions of gustatory disgust or

pleasure > neutral expressions as the contrast of interest for the concrete condition; and b) socially attributable interaction of geometric shapes > mechanical interaction as the contrast of interest for the abstract condition. The first level contrasts of experiment1 were then analyzed at the second level using a random effects analysis. We extracted right STS regional BOLD response values (percentage change) for each individual as elicited by concrete social cognition, and used these values as predictors of the same individuals' whole-brain BOLD responses to abstract social cues at the second-level.

Results: Viewing of concrete social cues resulted in BOLD response in bilateral STS, frontolimbic regions (bilateral amygdala, parahippocampal gyrus, midbrain and brainstem), as well as visual cortical regions, with the global maximum of activation being registered in the right STS [at MNI coordinate X, Y, Z = 54, −44, 20] at $p < 0.001$. The magnitude of BOLD response signals observed during viewing of gustatory facial emotions in the right STS, was found to be strongly predictive of the magnitude of BOLD response observed during abstract social attribution in the temporoparietal including STS, visual cortical areas, parahippocampal gyrus, bilateral amygdala and anterior insula, dorsolateral, dorsomedial and ventrolateral prefrontal cortices bilaterally at $p < 0.005$ FDR corrected.

Conclusions: Successful social information processing requires the intact functioning of a complex network of brain regions (Dolan, 2002; Adolphs 2010), but the neural signatures representing the human ability to decipher both concrete and abstract social signals remains largely undefined. Given the high prevalence of social cognitive dysfunctions such as autism and Fragile X syndrome coupled with a lack of well-defined neurobiological correlates of the associated social deficits, we took a novel developmental approach using the brain response patterns of the STS (a well-known social cognitive node) during concrete social cognition to predict regional BOLD response to abstract social cues. We showed that the magnitude of signal change in the right STS during concrete emotional processing was a strong predictor of the magnitude of an extensive network of sensorimotor and fronto-limbic regional response to abstract social cues in the same individuals. Such cross-task analyses, especially when combined with measures of social cognitive dysfunction in developmental cohorts, may hold promise for defining subtle network activation patterns that may serve as biomarkers for specific social cognitive dysfunctions in clinical populations such as autism spectrum disorder.

Keywords: STS, Social Cognition, Developmental, fMRI.

Disclosure: Nothing to Disclose.

W48. Dissociation of Hippocampally Mediated Relational Versus Item-specific Memory Deficits in Schizophrenia Using Eye-movement Monitoring During fMRI

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Background: Eye-movements can be used to index memory, as participants increase viewing of portions of a scene that change between study and test. These memory-based viewing effects have been characterized as relatively automatic, and can be outside conscious awareness, making this method particularly attractive for clinical studies where there may be concerns about task compliance or mental effort. Previously, we demonstrated that relative to healthy comparison participants (HC), individuals with schizophrenia (SZ) showed intact eye-movement-based memory effects when there was a change of a single item in the scene (item-specific memory), but were impaired when there was a relational change in the scene (e.g., the item moved from one location to another) (Hannula et al., 2010). The current study utilized the same paradigm during fMRI scanning to attempt replication and to identify neural correlates of spared (i.e., item-specific) and impaired (relational) memory. Because the hippocampus is necessary for relational memory representations, we hypothesized that any relational eye-movement memory impairments in SZ would be accompanied by hippocampal dysfunction.

Methods: 26 HC and 24 SZ participants were recruited from the UC Davis Early Psychosis Programs. Participants completed the memory task during fMRI on a 3 Tesla Siemens scanner at the UCD Imaging Research Center. Eye movements were recorded during fMRI scanning using an ASL remote eye-tracker installed in the scanner. During encoding, participants were asked to answer an item or relational question about a critical item in the scene. At test, participants viewed either an unchanged scene, a previously studied scene where the critical item is replaced with a new item, a previously studied scene where the critical item has changed location, or a novel scene, and were asked to indicate whether or not there had been a change in the scene or if it was new. The proportion of total viewing time directed to the critical item when scenes were manipulated (vs. not) was used to index memory, with increased viewing to changed regions representing a memory effect. fMRI preprocessing and statistical analyses were performed in FSL, contrasting changed scenes with unchanged scenes, and relational with item-specific changes. These contrasts were performed for a priori ROIs in the dorsolateral (DLPFC) and ventrolateral (VLPFC) prefrontal cortex, and in hippocampal (HI), perirhinal (PRc), and parahippocampal (PHc) ROIs within the medial temporal lobe (MTL). Significant effects were determined with one-sample and two-sample t-tests, employing a height-threshold of $z = 2.3$ ($p < .01$), cluster-corrected for multiple comparisons at $p < .05$.

Results: As in our previous work, participants in both the HC and SZ groups showed eye-movement-based memory effects for item-specific changes, but viewing time differences were only evident among HC participants when there was a relational change. HC individuals also showed greater HI, DLPFC, and VLPFC activation compared to people with SZ when correctly identifying relational changes. There were no significant between-group differences in fMRI activation when participants were correctly recognizing item-specific changes in the scene.

Conclusions: These combined eye-movement and fMRI results converge with previous studies in supporting the conclusion that individuals with SZ have the greatest difficulties with episodic memory when they must recruit hippocampal and PFC memory networks necessary for

forming inter-item or item-context relational memory representations. These relational memory difficulties may also help explain why individuals with SZ appear more impaired in recollection versus familiarity-based retrieval of previous events (see Libby et al., 2012). In contrast, episodic memory for specific item features appears to be a relative strength in people with SZ and may serve as a compensatory strategy that can be used to reduce the overall severity of memory dysfunction in the disorder.
Keywords: episodic memory, declarative memory.
Disclosure: None.

W49. Deficits at the Perception-Attention Interface in Schizophrenia: An fMRI Study

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Background: Individuals with schizophrenia consistently demonstrate impairments in early visual perception and attention. At the interface between these stages of processing, information is integrated and consolidated in a capacity-limited manner. Rapid serial visual presentation (RSVP) paradigms, in which items are displayed at the same spatial location in rapid sequence, have been used to probe this interface. Single-target RSVP tasks reflect general target detection capabilities, while dual-target tasks magnify the capacity-limited nature of later stages of information processing by requiring the RSVP stream to be monitored for two targets (T1 and T2). Behaviorally, these capacity limits appear to be exaggerated in patients with schizophrenia. Imaging RSVP studies of healthy adults implicate a temporo-fronto-parietal neural network in support of target identification and selection. However, the neural correlates of deficits in these processes in schizophrenia are not known.
Methods: Twenty-one clinically stable schizophrenia outpatients and 25 demographically matched healthy controls completed single- and dual-target RSVP tasks modified for event-related fMRI. In both tasks, uppercase letters served as targets and numbers served as distractors. For the dual-target task, a second target (T2), which was either an X or a Y, was presented at 3 lags after T1 (100ms, 300ms, and 700ms). Each trial was comprised of 20 stimuli (targets and distractors) presented for 85ms with an inter-stimulus interval of 15ms, followed by a 2500ms response period. The single-target task consisted of 34 trials; the dual-target task consisted of 34 trials of each lag presented in pseudo-randomized order across 4 runs. Imaging was performed on a Siemens 3-T Trim Trio scanner and data were analyzed using FSL software.
Results: Behaviorally, there was a main effect of group for both single- and dual-target tasks, such that patients identified fewer targets than controls. For the dual-target task, there was also a main effect of lag, with both groups showing an attentional "blink" indicated by poorer performance at lag 3 than lag 1 or lag 7; there was no group by lag interaction. fMRI analysis revealed that, during the single-target task, both groups activated bilateral frontal (inferior and middle frontal gyrus), parietal (posterior supramarginal gyrus, angular gyrus, superior parietal lobule), and temporal (posterior middle and inferior temporal gyrus) regions, as well as anterior cingulate cortex and lateral occipital complex. Direct group contrasts revealed greater task-related deactivation in patients compared to controls in anterior and posterior midline regions. To isolate the effect of adding a second target to the RSVP sequence and control for general target detection deficits, the dual-target task was contrasted against the single-target task. This contrast revealed largely overlapping regional activity patterns for patients and controls in bilateral frontal and parietal regions. However, patients showed greater activation in right supplementary motor cortex, pre- and post-central gyrus, as well as several occipital and temporal regions.
Conclusions: We utilized fMRI to identify regional brain activity associated with impaired performance on an RSVP paradigm in schizophrenia. Despite behavioral differences, patients and controls activated overlapping regions of bilateral frontal, parietal, temporal and occipital cortices during both tasks. However, patients exhibited a complex pattern of increased deactivation and activation that varied by task. Greater relative task-induced deactivation in schizophrenia during the single-target task may indicate increased effort, perhaps because patients work harder to suppress extraneous internal thoughts while focusing on the task at hand. In addition, hyperactivation during the dual-target task may reflect greater interference due to increased, but inefficient, responsivity to task stimuli. The current findings support the conclusion that schizophrenia patients are hyper-responsive when closely monitoring a series of rapidly-presented visual stimuli.
Keywords: schizophrenia, fMRI, cognition.
Disclosure: Dr. Michael Green has been a consultant to AbbVie, DSP, Forum, and Roche, and he is on the scientific advisory board of Mnemosyne. He has received research funds from Amgen.

W50. Single-stimulus fMRI Produces a Neural Individual Difference Measure for Autism Spectrum Disorder

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Background: Functional magnetic resonance imaging has become a working tool of cognitive neuroscience with a nearly exclusive focus on making inferences about neural substrates of cognitive phenomena at the group level. We report the use of a single-stimulus BOLD response in the middle cingulate cortex that differentiates individual children with autism spectrum disorder (ASD) from matched typically developing (TD) control children. The middle cingulate cortex is particularly responsive in cognitive processes related to perspective taking. Tomlin et al., showed in a social exchange experiment that activity in the cingulate cortex tracks the active agent (i.e., "me"

versus "not me") (Tomlin et al., 2006). Following this work, Chiu and colleagues demonstrated that a "self-response" in the middle cingulate cortex varied parametrically with symptom severity in the ASD cohort (Chiu et al., 2008). Chiu and colleagues also performed an eyes closed visual imagery experiment using 81 accomplished athletes and 27 healthy adults and found that the same pattern of activity (i.e., "self-response" in the middle cingulate cortex) could be elicited by taking a first-person perspective, but not during third-person perspective taking. Kishida et al., then showed a passive picture viewing task in healthy adults and showed in an adult cohort that the same middle cingulate cortex region-of-interest (ROI) in the visual imagery experiment differentiated pictures of "self faces" from pictures of "other faces". (Kishida et al., 2012). These results suggest that a similar picture viewing assay might elicit signals in this same ROI strong enough to produce a neural measure that might also differentiate children diagnosed with ASD from age- matched TD children.

Methods: 39 adults with no known neuropsychiatric disorders, 45 TD children and 27 children with ASD were recruited from the Houston metropolitan area and the Texas Children's Hospital's Autism Center. Photographs of subjects were taken prior to scanning. Individuals were scanned in a 3T Siemens Trio full body scanner while being shown 15 pictures of the subject ('self'), and 15 unique pictures of an age- and gender- matched individual ('other') for four seconds. Data were preprocessed and analyzed using the SPM8 software package. The hemodynamic time courses for the first presentation of each image, "self" or "other" were extracted and analyzed. Classification was performed using a penalized logistic regression with leave-one-out cross validation on the BOLD response to the first 'self' image, only. Notably, our method requires no averaging over stimulus presentations or individuals.

Results: Restricting our analysis to the first presentation of either "self" or "other stimuli allowed us to have a task length of under 2 minutes. Longer experimental paradigms reduce the cohort of individuals that were available for analysis. Unlike adult and TD subjects, ASD children showed significant head movement in the scanner. After 5 minutes of scanning time, over 40% of the data from the ASD population could not be analyzed to due excessive head movement (instantaneous movement threshold of $\pm$ 3.5mm). Reducing scanning time to less than 2 minutes, i.e. "single-stimulus" responses, allowed us to retain over 75% of the ASD participants. Using a leave-one-out cross–validation (LOOCV) penalized regression on the hemodynamic time series of the first "self" image produced a model with sensitivity and specificity of 63.6% and 73.7% respectively, and an AUC of 0.773. The selected model included covariates that emphasize not only the difference in amplitude in self-responses, but also differences in the relaxation and latency of the BOLD response. Methods to discriminate between TD and ASD children using only the peak of the BOLD response resulted in sensitivity and specificity of 54.6% and 57.9% respectively and an AUC of 0.591. Further, a similar analysis using only the first "other" hemodynamic response generated a ROC curve with an AUC of 0.607.

Conclusions: The clinical adoption of a magnetic resonance imaging (MRI) biomarker for psychopathology will require, at minimum, reliable and accurate classification of disease. Further, the success of any potential clinical diagnostic strategy also depends on operational reliability, reliability that often derives from simple and cost-effective procedures. Our work suggests that single- stimulus methodologies, in a MCC ROI that was previously identified in several hundred normal individuals in other "self" and "other" tasks (Chiu et al., 2008; King-Casas et al., 2005; Kishida, King-casas, & Montague, 2011; Tomlin et al., 2006), may provide accurate classification of disease in ASD patients. Further, BOLD time series data from simple and short paradigms, which had previously been thought to be highly smoothed and noise-ridden, may nonetheless provide useful diagnostic information. We are cautiously optimistic that this work may provide a small step toward developing MRI based applications for screening of psychopathology or other - more typical - cognitive phenotypes.

Keywords: fMRI, autism, methods.

Disclosure: Nothing to Disclose.

W51. Hippocampal Volume and Gender Differentially Predict Rumination in Adolescents at Risk for Depression

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Background: Vulnerability to depression is heightened in adolescence when substantial change occurs in brain regions related to depression (e.g., hippocampus, amygdala, and striatum). Depression is also experienced at higher levels by females than males, particularly by adolescence. Indeed, adolescent brain structure has been linked to sex differences in depression. For example, larger bilateral hippocampus predicted increased depression in girls but not boys with highly aggressive mothers (Whittle et al., 2011). Examining cognitive-affective response styles in relation to brain regions that are sensitive to emotions and stress, and involved in repetitive behaviors and memory may elucidate mechanisms of sex-differences in adolescent depression. One cognitive-affective dimension of depression worthy of examination is rumination, the tendency to think repetitively and passively about one's negative emotions. The current study examined the role of hippocampal, amygdala, and striatal volume in determining sensitivity to sex-related differences in rumination. Furthermore, despite an overall increase in depression onset during adolescence, adolescents of Mexican-origin experience higher rates of depression relative to peers of other ethnic/racial groups; thus, we examined these associations in a sample of Mexican-origin adolescents at-risk for depression.

Methods: Participants included 174 Mexican-origin adolescents (53% female, age = 16-17 years) selected from a large community study based on having an elevated major depressive disorder symptom count on the Diagnostic Interview Schedule for Children-IV (Shaffer et al., 2000) and/or elevated scores on the Anhedonic Depression and/or General Distress scales of the Mood and Anxiety Symptom

Questionnaire (Watson & Clark, 1991). Rumination was measured using the Rumination Scale (Treynor, Gonzalez, & Nolen-Hoeksema, 2003), which has 22 self-report items (e.g., how much do you generally think about how sad you feel?) rated on a 4-point scale from 1 = almost never to 4 = almost always. Structural magnetic resonance images were acquired using an MPRAGE sequence. Brain volumes were calculated and corrected for total brain volume in four subcortical regions of interest (ROI) implicated in adolescent depression, including bilateral amygdala, bilateral hippocampus, bilateral nucleus accumbens, and bilateral caudate. Left and right volumes were averaged for each ROI. To test respective contributions of each ROI to rumination, linear regression analysis was used to predict rumination scores based on gender, the four ROI volumes, and the interaction term of gender and each of the four ROI volumes. ROI volumes were mean centered. Age and IQ were initially included, but removed from the final analysis due their non-significant contributions (coefficient p-values: .76-.96).

Results: The overall regression model was significant ($F_{9, 164} = 2.17$, $p = .049$).Rumination was significantly predicted by the interaction term between hippocampal volume and gender ($t = 2.12$, $p = .036$, Beta = .299), indicating that females with larger hippocampal volumes had higher levels of rumination whereas males did not vary in rumination as a function of hippocampus volume. The interaction between caudate volume and gender was at a trend significance level ($t = 1.92$, $p = .057$, Beta = .25). Thus, as with hippocampus, girls with larger caudate volumes had higher levels of rumination. Gender alone was at a trend significance level ($t = 1.80$, $p = .073$, Beta = .14). Amygdala ($p = .36$) and nucleus accumbens ($p = .50$) volumes did not significantly predict rumination as a main effect or by gender.

Conclusions: Mexican-origin girls with larger hippocampus and caudate may be at heightened vulnerability to depression through ruminative thought processes. Although these data are cross-sectional and correlational, the findings suggest that a larger hippocampus and larger caudate may reflect dysfunction in neural circuits that support memory and repetitive behaviors. Future work should include longitudinal assessments of brain structure, rumination, and depression to better understand the mechanistic pathways to depression in adolescence.

Keywords: adolescence, depression, brain volume, rumination.

Disclosure: Nothing to Disclose.

W52. Cognitive Dysfunction in Geriatric Bipolar Disorder and Major Depressive Disorder

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Background: Bipolar disorder (BPAD) and Major depressive disorder (MDD) are prevalent in the geriatric population and are chronic and disabling illnesses with medical and psychiatric co-morbidities. Cognitive changes are common in these disorders and are associated with increased functional impairment and poor quality of life, particularly in elders with BPAD and MDD. The purpose of the present study was to examine different domains of cognitive function in geriatric BPAD and MDD and to investigate the effects of illness severity on cognitive function. An additional objective was to compare patterns of cognitive function across the two disorders in order to gain insight into underlying neurobiology that could guide targeted interventions.

Methods: A total 129 subjects with BPAD type I (n = 48) or MDD (n = 37) age > 65 (mean age: 67.1 years, standard deviation: 1.2 years) were recruited from the McLean Hospital Geriatric Psychiatry Outpatient program, from other Harvard hospital outpatient programs, and from Boston area advertisements. Inclusion criteria included a DSM-IV-TR diagnosis of BPAD type I or MDD. Subjects were excluded if they had a diagnosis of dementia, cognitive disorder NOS, a Mini-Mental State Examination score < 24, active substance use disorder, or if they had had electroconvulsive therapy in the past six months. All subjects underwent clinical assessment that included measures of mood (Montgomery-Asberg Depression Rating Scale, Hamilton Depression Rating Scale 17) and medical co-morbidity (Clinical Illness Rating Scale (Geriatric) (CIRS(G)). Subjects additionally underwent a neuropsychological assessment with tasks that measured verbal fluency, visual confrontation naming, executive function, working memory, processing speed, and short-term recall including the FAS task, the Category task, Boston Naming Test, Trails A and B, Wisconsin Card Sorting Task, Stroop Interference Task and CERAD word list task. Results of subjects with mood disorders were compared to those of a group of mentally healthy elders (n = 44; mean age 65.6, standard deviation: 1.3 years) by multiple linear regression with Bonferroni correction; age, gender, education, depression severity, medication burden (chlorpromazine and benzodiazepine equivalents) and medical illness burden were included as covariates. Statistical analyses were carried out using JMP Pro 11 Software (SASS instrument, Cary, NC).

Results: Subjects with BPAD and MDD were significantly impaired relative to healthy elders across multiple cognitive domains including processing speed, executive function, verbal fluency and short-term recall ($p < 0.01$ across all tasks). Diagnosis remained a significant predictor of performance after age, gender, education, depression severity and medication and medical illness burden were included as covariates. Medication burden (chlorpromazine equivalent and benzodiazepine equivalents) as well as depression severity independently predicted performance on tasks of processing speed, but not other cognitive tasks. Subjects with BPAD performed significantly worse than controls relative to subjects with MDD on a task of phonemic fluency. Subjects with MDD performed significantly than controls relative to subjects with BPAD on tasks of semantic fluency and short-term recall.

Conclusions: Elders with BPAD and MDD have impaired cognitive function relative to healthy elders in several

cognitive domains. Moreover, depression severity and medication burden independently predict performance on tasks of processing speed. These findings also suggest that there may be a distinct pattern of cognitive deficits across geriatric BPAD and MDD. A differential deficit in semantic fluency and short term recall in MDD may reflect greater impairment in semantic memory, similar to what has been observed in Alzheimer's dementia, while a differential deficit in phonemic fluency in BPAD may in part reflect compromise of executive function. These findings and future work may clarify the underlying neurobiology of BPAD and MDD and influence both the choice of clinical interventions and ultimately outcome. They may also shed light on the relationship between geriatric mood disorders and dementia.
Keywords: Bipolar Disorder, Depression, Geriatric, Cognition.
Disclosure: Nothing to Disclose.

W53. Executive Function and Behavioral Outcomes in Adults Born Prematurely

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Background: Survival rates for infants born very preterm (<32 weeks gestation) and extremely preterm (<28 weeks gestation) have increased over the past decade. Gestational length has been found to have a profound effect on children's cognitive development and behavior. The impact of preterm birth on behavioral and neurocognitive trajectories, including the development of executive function in children born very and extremely preterm, have not been adequately followed into adulthood. The aim of this presentation will be to address this gap in the literature.
Methods: We acquired neuropsychological measures of executive function (as measured by a broad EF battery: the Delis-Kaplan Executive Function System, with measures of flexibility, letter fluency, category switching, inhibition, problem-solving skills, spatial planning, inhibition of impulsive/perseverative responding, and rule learning) in 14 age- and IQ-matched adults born extremely preterm (<28 weeks gestation) between the ages of 18-35. Adults born preterm were compared to typically developing adults. Data were analyzed by $\chi 2$ or standard analysis of variance (ANOVA) techniques.
Results: Preliminary results show group differences in inhibition and rule learning, with adults born extremely preterm exhibiting impairments in both realms of executive function, even when adjusting for age.
Conclusions: Our results suggest that adults born extremely preterm display deficits in tasks associated with specific hallmarks of executive functioning. Future diffusion tensor imaging research will aim to address the white matter differences that may be responsible for causing such deficits.
Keywords: Prematurity, Executive Function.
Disclosure: Nothing to Disclose.

W54. The Utility of P300 as a Schizophrenia Endophenotype and Predictive Biomarker: Clinical and Socio-demographic Modulators in COGS-2

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Background: Reduced auditory P300 amplitude is a robust schizophrenia deficit exhibiting the qualities of a viable genetic endophenotype. These include large heritability, high test-retest reliability, and relative trait-like stability in the face of fluctuating symptoms and treatment. Recent evidence suggests that P300 may also serve as a predictive biomarker for transition to psychosis during the schizophrenia prodrome. However, historically, the utility of the P300 as a disease biomarker has been limited by its clinical nonspecificity and cross-site measurement variability. It's utility has also been constrained by the need for specialized evoked potential laboratory equipment and expertise. The Consortium on the Genetics of Schizophrenia (COGS) study provided an opportunity to examine the consistency of this measure using very simple standardized hardware, across multiple sites with varying degrees of EEG experience. The large sample size also offered the opportunity to identify important modulating factors that might contribute to measurement variability.
Methods: Auditory P300 data were acquired from 789 controls and 888 schizophrenia patients at 5 sites, using a simple 2-channel turnkey stimulus delivery and EEG recording device. P300 amplitude was measured from the average ERP waveform response to an identified target tone. Data quality and group differences were assessed across sites, and the impact of various socio-demographic moderating factors, including site, race, smoking and substance use, was assessed.
Results: Of the 1677 initial EEG recordings, 1236 (74%) were deemed to have valid, reliably measureable, P300 responses. Relative data loss across sites was unrelated to the level of prior EEG expertise. An overall patient P300 amplitude deficit was observed, with effect size of 0.62. Each site independently observed a significant patient deficit, but significant across-site differences in amplitudes and effect sizes also existed. In patients, these site differences reflected clinical sampling differences in positive symptomatology and functional capacity. In controls, the site differences reflected differences in racial stratification, smoking and substance use history. Being African American with a past history of substance abuse or dependence, or being an active smoker, resulted in a reduced P300 response. However, these factors suppressed P300 amplitude in control subjects, but not in patients. This differential impact resulted in an attenuated patient-control difference (i.e., smaller effect size) when both groups included smokers or African Americans with a history of substance use.

Conclusions: These findings indicate that the P300 can be adequately assessed quantitatively, across sites, even in clinical settings where substantial EEG expertise and equipment may be lacking. Measurements that are suitable for both genetic endophenotype analyses and studies of psychosis risk and conversion can be quickly and readily obtained. However, comorbid factors such as smoking and substance use also modulate P300, and these have a selective impact on P300 amplitude in healthy control subjects. The selectivity of this effect presumably reflects the fact that P300 amplitude is already suppressed by illness in schizophrenia patients – i.e., a "floor" effect. This raises an important cautionary note with respect to using the P300 as a disease biomarker. Careful attention must be given to the selection of appropriate comparison samples to avoid misleading false negative results.
Keywords: Schizophrenia, P300, Endophenotype, COGS.
Disclosure: Nothing to Disclose.

W55. Cortical Systems Underlying Perception of Basic Visual Motion and Perception of Biological Motion in Schizophrenia: Findings from Noise Paradigms

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Background: Perception of biological motion and perception of basic visual motion, two critical visual and cognitive capacities for social functioning, are impaired in schizophrenia. It is not well understood whether the impaired behavioral capacities are due to altered processing in the cognitive system such as the Superior Temporal Sulcus (STS) that mediates biological motion perception, or in the sensory system such as the Middle Temporal Area (MT) that mediates basic visual motion perception, or in both.
Methods: For both biological motion (BM) and basic visual motion (VM), we examined brain activations using a noise paradigm in which motion signals were presented according to perceptual capacities of each participant. Perceptual threshold was first determined psychophysically for schizophrenia patients ($n = 20$) and healthy controls ($n = 20$). Functional MRI was then acquired while the participants performed the biological motion and basic visual motion tasks under the perceptual threshold condition (a minimally required signal) and under the 100% condition (a maximally available signal).
Results: In MT, schizophrenia patients showed lower activations during performance of VM for the non-salient stimuli (perceptual threshold) and during performance of BM for both salient (100%) and non-salient stimuli. Similar MT activations in the two groups were observed during performance of VM for salient stimuli. In STS, patients showed lower activations during performance of BM for both salient and non-salient stimuli. During performance of VM, minimal STS activations were observed in the two groups.
Conclusions: The pattern of results suggests weakened sensory processing of basic visual motion in schizophrenia. Impaired biological motion perception in this mental disorder may be due to both sensory processing and cognitive processing factors, especially in the presence of non-salient motion signals. This finding highlights the importance of increasing the saliency of sensory signals in the improvement of patients' social cognitive functioning.
Keywords: cognition, perception, brain imaging, schizophrenic.
Disclosure: Nothing to Disclose.

W56. Effects of NMDA Receptor Antagonism on High Frequency Neuronal Oscillations and Working Memory Performance in Cynomolgus Macaques

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Background: Disruptions in sensory processing and abnormal temporal integration of neuronal oscillations, especially within the gamma frequency range (30-80 Hz), have been identified in schizophrenic patients during working memory tasks and may contribute to the poor performance within this cognitive domain. Experimentally, alterations in gamma oscillations, as well as the induction of other schizophrenia-like symptoms including cognitive deficits, can be induced in rodents, non-human primates (NHPs) and humans with NMDA receptor antagonists (e.g., phencyclidine [PCP], ketamine). Given that NHPs and humans both have highly-evolved prefrontal cortical structures that mediate working memory processes our objective was to investigate the effects of acute and sub-chronic PCP treatment on neuronal oscillations and event-related potentials (ERPs) in cynomolgus macaques performing a delayed-match-to-sample (DMTS) working memory task.
Methods: Macaques ($n = 8$) were trained to match a sample stimulus following a delay period on a touchscreen in exchange for food rewards. Subsequently, all subjects were implanted with EEG electrodes [placed on the dura mater above the frontal cortex (FC) and primary visual cortex (V1)]. For the acute studies, NHPs ($n = 7$) were treated with PCP (0, 0.03, 0.056, 0.1 mg/kg) using a cross-over study design, while for the sub-chronic studies, two cohorts of animals ($n = 4$/group) were treated with PCP (0 or 0.3 mg/kg) twice daily for 14 days. The effects on DMTS performance and high frequency EEG oscillations were assessed following both treatment regimens.
Results: In the acute study, PCP dose-dependently decreased DMTS performance accuracy. EEG analyses acquired during DMTS performance demonstrated a significant elevation in the post-stimulus amplitude of low (30-50Hz) and high gamma (51-80 Hz) oscillations by PCP in both the FC and V1 regions during correct responses. In addition, PCP significantly prolonged the cognitively-relevant P300 component of the mean ERP during correct responses in FC. Preliminary results from the sub-chronic dosing study indicated PCP-treated animals were less impaired on DMTS performance accuracy across delay intervals than in the acute study. However, animals treated sub-chronically with PCP showed a significantly greater number of omissions at the more cognitively-demanding

longer delays compared to the vehicle-treated animals. The analysis of the corresponding EEG is currently ongoing.
Conclusions: Overall, our results suggest that acute administration of a NMDA receptor antagonist disrupts neuronal oscillations and cognitive processing, especially in the FC, and this may contribute to the observed cognitive impairment in macaques. In contrast, sub-chronic PCP treatment produces less impairment on delay-dependent working memory accuracy, although macaques were much more likely to omit difficult trials possibly suggesting a decrease in motivation at higher cognitive demands. These studies may help to define the role of high frequency oscillations in cognitive processes in higher order species, and to enhance our understanding of them as a translatable biomarker for cognitive impairments associated with schizophrenia.
Keywords: working memory, monkey, EEG, gamma oscillations.
Disclosure: Work presented is funded through F. Hoffmann LaRoche postdoctoral fellowship; E.B. and D.A. are employees of F. Hoffmann LaRoche, Ltd.

W57. Physiological Indicators of Multisensory Facilitation of Visual Responses in Schizophrenia

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Background: Auditory and visual deficits have been consistently reported in patients with schizophrenia, with more recent studies providing evidence of both direct and indirect influences of sensory deficits on cognitive abilities. However, real-world interactions are multisensory in nature. Thus, investigations into the underlying mechanisms associated with multisensory integration, while uncommon, are also warranted. The few multisensory studies that have been performed in schizophrenia have provided inconsistent results. Yet, based on these studies and the poor connectivity hypothesis of schizophrenia, we hypothesized that patients with schizophrenia (SP) would show impaired multisensory integration relative to healthy controls (HC). However, in our previous EEG study (Stone et al. 2011), we identified improved auditory function in SP in response to multisensory stimuli relative to auditory stimuli alone. This was accompanied by improvement in multisensory behavioral reaction times relative to unisensory reaction times. To determine the generalizability of our previous results, we followed up our EEG study with this MEG study to further investigate multisensory integration in schizophrenia using source analysis.
Methods: We recruited 57 patients with schizophrenia and 62 healthy control participants. We investigated multisensory responses using a forced choice auditory/visual multisensory paradigm, where participants responded to spatial location of unisensory auditory, unisensory visual and simultaneous auditory and visual stimuli in a fully randomized design. Auditory stimuli were simple 1000 Hz tones and visual stimuli were black and white soccer balls presented within a perspective drawing of a soccer field. During the task, the participants were required to fixate on the goalie and respond to each stimulus (A, V and AV) to determine if the stimulus was near or far within the perspective drawing. Behavioral reaction times were recorded during MEG data acquisition. Evoked responses were measured using an Elekta Neuromag 306 channel MEG system, and were preprocessed to remove artifacts. Source analysis was performed using CSST (Ranken et al. 2004) and the resulting source locations and timecourses were evaluated. For our current analysis, we identified the peak latencies of the timecourses from dipole sources in visual cortex in response to unisensory visual and multisensory stimulus conditions.
Results: SP and HC groups were matched on age and gender. The mean age by group was 38.1 (SEM – 1.8) years – SP and 35.7 (SEM – 1.4) years for HC. Based on a mixed-model, repeated-measures design, a significant interaction ($p = 0.001$) of group (SP versus HC) by condition (unisensory visual stimuli, multisensory stimuli) was identified. Consistent with behavioral results indicating greater multisensory facilitation in SP relative to HC, SP (165 ms) had slower visual peak latencies relative to HC (154 ms) in response to unisensory visual stimuli yet faster (SP – 148 ms) visual peak latencies than HC (153 ms) in the multisensory condition, indicating facilitation of the cortical visual response.
Conclusions: This result is consistent with our previous studies indicating a similar facilitation of the multisensory evoked auditory response relative to the unisensory evoked response in SP relative to HC. Contrary to our initial hypothesis, the results indicate that individuals with schizophrenia may compensate for unisensory deficits through multisensory stimuli. Furthermore, our source analysis results suggest that the facilitation occurs at the early sensory processing level and may help explain the facilitation of reaction times in patients with schizophrenia. Instead of implicating poor connectivity at the multisensory integration level, the results may provide support for the high noise model of schizophrenia. In this case multisensory stimuli may help improve the fidelity of the sensory information thereby facilitating the sensory response to the extent that behavioral responses are normalized relative to healthy controls. Future studies are needed to determine if cognitive training may benefit from multisensory presentation of information to help circumvent sensory processing deficits in SP.
Keywords: MEG, multisensory, schizophrenia, visual cortex.
Disclosure: Nothing to Disclose.

W58. Gq Signaling in Perirhinal Cortex Reverses Methamphetamine-induced Recognition Memory Deficits

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Background: Long-term methamphetamine (meth) abuse has been linked to certain cognitive impairments in humans. In rats, chronic meth self-administration leads to deficits in novel object recognition memory, which relies upon the perirhinal cortex. We find numerous neuroadap-

tations in this region after long-access meth, including a reduction in membranous mGlu5 receptors. These mGlu5 receptors are coupled to Gq-mediated intracellular signaling, and they play an integral role in object recognition memory. Here we tested weather perirhinal Gq signaling would repair the chronic meth-induced memory deficits.
Methods: Male, Sprague-Dawley rats self-administered meth (0.02 mg/infusion, i.v.) along an FR1 schedule of reinforcement. After 7 daily 1-h sessions, rats were switched to 6-h daily access sessions for 14 days, and then underwent drug abstinence. On abstinence days 7 and 8 (90 min and 24 hr tests, respectively), rats were tested for object recognition memory using a two-item object recognition task. In Experiment 1, we used a new positive allosteric modulator (PAM), 1-(4-(2,4-difluorophenyl) piperazin-1-yl)-2-((4-fluorobenzyl)oxy)- ethanone, or DPFE, to activate mGlu5 signaling in perirhinal cortex. DPFE demonstrates enhanced solubility compared to previous mGlu5 PAMs (e.g. CDPPB), thus enabling intracranial use with greater selectivity for mGlu5. We infused DPFE (0.5 μg/side) or vehicle (20% 2-hydroxypropyl-β-cyclodextrin) bilaterally into the perirhinal cortex immediately after object familiarization. Ninety min and 24-h later, rats underwent a short-term and long-term memory test to assess novel object recognition. In Experiment 2, we used a viral-mediated gene transfer approach to infect perirhinal neurons with a designer drug (DREADD) of the hM3Dq variant, which couples to endogenous Gq signaling intracellularly, thus emulating mGlu5 signaling through Gq. Rats were infused with AAV2-hSyn-HA-hM3Dq-IRES-mCitrine vector (UNC Vector Core) bilaterally into the perirhinal cortex prior to meth self-administration, therefore allowing at least 4 weeks for Gq-DREADD expression to peak. Using consistent timepoints described above, the Gq DREADD was activated by administering the designer drug clozapine-N-oxide (CNO, 10 mg/kg, i.p.).
Results: Chronic meth self-administration resulted in an escalation of meth intake over time and pronounced short- and long-term object recognition memory deficits. Both DPFE and CNO effectively restored object recognition memory in meth rats on the short-term memory test. On the long-term test, however, the therapeutic effects were no longer evident.
Conclusions: The data suggest that mGlu5 receptor activation and/or activation of Gq signaling within the perirhinal cortex is capable of restoring memory deficits resulting from long-access meth exposure. However, these therapeutic effects were only evident in the short-term, when DPFE and CNO were biologically active, suggesting an effect on the expression of recognition memory, but not its consolidation. Thus, chronic administration of these compounds during abstinence may be necessary for achieving optimal cognitive function. Further studies will determine whether tolerance develops to mGlu5 activation with DPFE, as well as sustained Gq signaling activation with repeated CNO. Viral-mediated gene transfer of DREADDs to specific brain regions is an attractive way to activate or inhibit neurons within discrete neural circuits, and it permits chronic treatment systemically (with CNO) as opposed to repeated intracranial infusion, which is not clinically feasible. Restoring cognitive function in meth addicts, using these approaches, may aid inhibitory control and help maintain abstinence.
Keywords: DREADD, methamphetamine, memory, perirhinal cortex.
Disclosure: Nothing to Disclose.

W59. mGluR2/3 Agonism Restores Ethanol Dependence-induced Deficits in Contingency-mediated Behavior

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Background: The development of alcohol use disorders is known to be associated with loss of behavioral control. In particular, the ability to regulate drug-seeking and –taking is impaired in addicted individuals. While the transition from casual, goal-directed actions to inflexible habit-like behaviors is known to occur in healthy individuals, data suggest that the development of behavioral inflexibility is exacerbated in alcohol-dependent individuals (Sjoerds et al., 2013). A growing and significant literature suggests that chronic alcohol (ethanol) exposure results in dysregulation of corticostriatal glutamate signaling (e.g., Griffin et al., 2013; Meinhardt et al., 2013). In particular, it has been observed in both humans and animal models that chronic alcohol results in a down-regulation of mGluR2 mRNA in infralimbic cortical projection neurons. The loss of mGluR2 receptors on projection neurons likely results in increased glutamatergic tone in subcortical targets, including the nucleus accumbens where this has been observed to contribute to escalated alcohol drinking following chronic intermittent ethanol (CIE) exposure (Griffin et al., 2013). These data suggest that regulation of mGluR2/3 signaling may be a viable target for restoration of drug-induced deficits.
Methods: A mouse model of ethanol dependence involving repeated cycles of CIE exposure was used to investigate a causal role for ethanol exposure in the development of contingency-insensitive behavior, as well as a role for mGluR2/3 signaling in the expression of these behaviors. Adult male C57BL/6J mice were trained to self-administer 10% unsweetened ethanol on a fixed ratio 1 (FR1) schedule. After acquisition, mice were assigned to either a CIE vapor exposure group, or air-exposed controls (AIR). Mice in the CIE group were exposed to two weekly cycles (16 hr/day x 4 days) of chronic intermittent ethanol vapor exposure via inhalation. After exposure to CIE, mice were assigned to one of two experimental groups to separately investigate the effects of CIE on stimulus-outcome (S-O) and action-outcome (S-O) mediated behaviors. Mice for the A-O studies were retrained on an FR1 schedule for 2 days and then moved to a random interval 30 seconds (RI30) schedule for two days as this schedule has been shown to promote habit –like responding. Assessment of the ability to use action-outcome contingencies to guide behavior was performed using a contingency degradation procedure in which the relationship between the action and outcome was disrupted through provision of noncontingent reinforcement. To investigate the role of mGluR2/3 signaling in these behaviors, mice received either an injection of the mGluR2/

3 agonist LY379268 (1 mg/kg, i.p.) or saline 30 min prior to testing. Separate mice were trained in a S-O acquisition paradigm in which they learned that a particular stimulus (tone) was predictive of reinforcer delivery (sucrose). Tones were presented on a fixed time schedule, but reinforcers were delivered on a random time schedule only during cue presentation. Mice were trained in this paradigm for 8 days. Rescue of CIE-induced deficits by enhanced mGluR2/3 signaling was assessed through administration of LY379268 as described above. Data were analyzed using SPSS through the use of repeated measures ANOVA (rmANOVA) and t-tests as appropriate.

Results: CIE exposure resulted in decreased ability to use either A-O or S-O contingencies to mediate behavior. CIE-exposed mice were insensitive to the change in A-O contingency in the degradation session while AIR mice reduced responding ($p = 0.05$, $n = 10$/group). In addition, CIE mice were impaired in the ability to use a new S-O association to guide reward seeking. A rmANOVA indicated that across acquisition of the S-O behavior, CIE mice consistently showed lower licking behavior during the tone relative to air-exposed mice ($F1,34 = 4.186$, $p < 0.05$). Interestingly, both behaviors could be restored through the administration of LY379268. Administration of LY379268 prior to a contingency degradation session restored sensitivity to the change in contingency in CIE-exposed mice ($p < 0.05$). In addition, mGluR2/3 agonism resulted in increased discrimination between cue and inter-cue intervals in a Pavlovian training session ($F1,25 = 3.966$; $p = 0.057$).

Conclusions: Together, these findings demonstrate that CIE exposure impairs the ability to use newly acquired or changing contingencies to guide behavior. CIE resulted in impairments in flexible ethanol seeking, as well as impairments in the ability to use a stimulus-outcome association to drive food seeking. Moreover, both deficits could be restored through administration of an mGluR2/3 agonist, suggesting that a decrease in glutamatergic tone may enhance contingency-mediated behaviors in dependent animals. Indeed, work from other groups has indicated that enhancing mGluR2 expression on prefrontal projection neurons can restore ethanol extinction after chronic ethanol exposure. Ongoing work is investigating the neuroanatomical locus of this effect as well as CIE-induced alterations in the neurocircuitry that drives contingency-mediated behaviors.

Keywords: alcohol, glutamate, habit, behavior.
Disclosure: Nothing to Disclose.

W60. Higher Trait Anxiety is Associated with Decreased Reward Response During Delay Discounting in Women Recovered from Anorexia Nervosa and Bulimia Nervosa

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Background: The defining characteristic of an eating disorder (ED) is abnormal eating-related behavior that results in altered consumption of food. Individuals with anorexia nervosa (AN) lose weight and become emaciated by severely restricted dieting, whereas individuals with bulimia nervosa (BN) alternate between restricting and episodic binge eating and/or purging. Both AN and BN also experience elevated anxiety, regardless of whether they are ill or remitted. What accounts for such extremes of eating behaviors? Emerging evidence suggests that EDs are associated with alterations in corticostriatal limbic and dorsal cognitive neural circuitry that can make drugs and food rewarding, but that also engage self-control mechanisms to inhibit their consumption. We examined whether an enhanced sensitivity to anxiety may contribute to a shared deficit in valuation of reward that may underlie disordered eating. This study aimed to: 1) determine whether women remitted from AN (RAN), women remitted from BN (RBN), and control women (CW) differ in their response to hunger and satiety during delay discounting, a task requiring choosing between smaller-sooner or later-larger rewards, and 2) elucidate the relationship between anxiety and brain response in regions involved in reward-based decision making. Only adults who were remitted from AN or BN were studied to avoid the confounding effects of malnutrition and weight.

Methods: We used fMRI to investigate brain activation during delay discounting in 27 RAN (19 pure restricting subtype, 8 restricting-purging subtype), 30 RBN (11 pure BN, 18 BN with a prior episode of AN, 1 binge-eating purging AN subtype) and 21 demographically matched CW when hungry (after 16 hours of fasting) and when satiated (after being fed 30% of daily caloric needs). To determine whether choice behavior differed among the three groups, a Group (RAN, RBN, CW) $\times$ Visit (Hungry, Satiated) $\times$ Percent Monetary Difference linear mixed effects (LME) analysis was computed in R. Statistical analyses of fMRI data were performed using 2 separate general linear models (GLMs). To model brain reward valuation response, the first GLM included only decision trials in which the early reward option was available immediately (i.e., "Today"). To model cognitive control response, a second GLM included all decision trials. Regions of interest (ROIs) associated with reward valuation included the ventral striatum, dorsal caudate, anterior cingulate, and posterior cingulate. ROIs associated with cognitive control included the superior parietal cortex, middle frontal gyrus, insula, and ventrolateral prefrontal cortex. We employed a Group $\times$ Visit LME analysis in R for the valuation and cognitive models separately within their respective ROIs. Exploratory Huber robust regressions were conducted to examine the relationship between trait anxiety and blood oxygen level dependent (BOLD) response for valuation and cognition models during the Hungry and Satiated visits within the respective ROIs. Small volume correction was determined with Monte-Carlo simulations, giving an a posteriori ROI-wise of $p < 0.05$ for all comparisons.

Results: No significant differences were found in choice behavior. For valuation circuitry, a significant Group x Visit interaction within the bilateral caudate, anterior cingulate, posterior cingulate, and the right ventral striatum was found. Post-hoc analysis revealed CW had greater reward response when hungry relative to when satiated. RAN had greater response than CW when satiated, but within-group

comparisons revealed their brain response did not differ between hunger and satiety. RBN also had greater response than CW when satiated in the bilateral anterior cingulate. For cognitive circuitry, only the left insula and superior parietal cortex demonstrated a Group x Visit interaction. Post-hoc analyses revealed RBN had greater response than CW when satiated and greater response than RAN when hungry in the left insula. RBN also had greater response in the left superior parietal cortex when satiated than when hungry. For all valuation ROIs, there was a negative relationship between trait anxiety and BOLD response in ED participants, regardless of diagnosis, and regardless of hunger or satiety. In comparison, there was a positive relationship between trait anxiety and BOLD response in CW for all valuation ROIs, but only when satiated. Only CW showed a relationship between anxiety and BOLD response in cognitive ROIs: regardless of satiety, higher trait anxiety was associated with greater BOLD response in the left superior parietal lobe. When satiated, CW had elevated responses in the left insula with lower trait anxiety.
Conclusions: We extended our prior findings in RAN by showing that RBN are also less sensitive to the motivating influence of hunger on brain response to reward. More importantly, increased anxiety was associated with decreased brain response to reward valuation only in the ED groups, regardless of diagnosis and hunger or satiety. An enhanced sensitivity to anxiety may contribute to a shared deficit in valuation of reward that underlies dysfunctional approach/avoidance behavior and could account for both restricted eating and episodic overconsumption. Understanding the neurobiology of ED is critical for developing more effective treatments.
Keywords: eating disorders, delay discounting, fMRI, reward processing.
Disclosure: Nothing to Disclose.

W61. D1-Type Receptor Availability Supports Behavioral Flexibility in Healthy Humans: Examination of Post-error Performance Variation

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Background: Appropriate adjustment of behavior following error detection is an indicator of adaptive ability and is often compromised in patients with psychiatric conditions (e.g., OCD, schizophrenia, substance dependence). Performance flexibility following errors is often an indicator of exploratory behavior that is essential for adapting to changing environmental situations. Although the dopamine system has been implicated in various cognitive control processes important for behavioral flexibility, such as response inhibition and re-learning (e.g., reversal learning), the relationship between performance variation, as an indicator of behavioral flexibility, and dopamine has been underexplored. Flexible behavior may be examined in the context of a response-inhibition task by examining the variability in response times (RTs) during Go trials directly after response- inhibition errors occur. Post-error slowing is often observed during such trials; however, the variability in RTs is rarely examined, despite its suitability as an indicator of behavioral flexibility.
Methods: We examined the relationship between post-error response-time variability during the Stop-signal Task and both striatal D1- and D2/D3-type receptor availability in 22 healthy human volunteers. The standard deviation of response times on Go trials following unsuccessful stop trials was used as a measure of post-error performance variability. Positron emission tomography (PET), with 11C-NNC-112 and 18F-Fallypride as radiotracers, was used for assessment of D1- and D2/D3-type receptor availability, respectively.
Results: We found a positive correlation between post-error RT variability and D1 receptor availability in the associative striatum (ventral caudate and putamen), but no relationship in the sensory-motor striatum (dorsal caudate and putamen), indicating specificity to regions within the striatum that are important for learning. Moreover, no relationship was observed between striatal D1 receptor availability and variability of Go RTs following Go trials, suggesting that the relationship is specific to post-error adjustment of behavior. No significant relationships between RT measures and striatal D2/D3-type receptor availability were observed.
Conclusions: These results indicate that D1-type receptors within striatal regions that serve associative processing (e.g., reward learning) are important for performance flexibility that underlies adaptive behavior.
Keywords: dopamine, behavioral flexibility, PET, response inhibition.
Disclosure: Nothing to Disclose.

W62. Amphetamine Improves Human Attention Measured Using the Reverse-translated 5-Choice Continuous Performance Test

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Background: Impaired cognitive functioning occurs in numerous psychiatric disorders and is a core component of poor functional outcome. Impaired attention is so widespread that the recent RDoC initiative identified attention as one of the primary constructs deleteriously affected across psychiatric disorders. Hence, studies investigating the mechanisms underlying attention, how these mechanisms are affected in patients, and using these mechanisms to develop targeted treatments are urgently needed for psychiatric research. Utilizing animals in research is key to developing an in-depth understanding of the biology underlying human-relevant attentional function. The bridge between animal and human cognition has been the bottle-neck that has stalled treatment development. In response, to this need, we developed the 5-choice continuous performance test (5C-CPT) for testing attention in both rodents and humans and have provided evidence of its construct validity across species. Here, we assessed the predictive validity of the 5C-CPT by testing the hypothesis that amphetamine (AMP) would improve

attentional functioning in humans in a dose-dependent manner.
Methods: We investigated the effects of a acute doses of AMP on performance of the 5C-CPT in a double-blind, placebo-controlled study. Healthy subjects (aged 18-35) were assigned randomly to receive a single 10 mg or 20 mg dose of AMP or placebo ($n = 18$ per group). Subjects were in good general health, no lifetime history of an Axis 1 or II disorder, with no first-degree relatives with a history of psychotic or mood disorders. Attentional testing commenced 4 hours after ingestion of AMP using the 5C-CPT. The 5C-CPT requires subjects to use a joystick and respond to single circles (target stimulus) but inhibit from responding when 5 circles appear (non-target stimulus). Performance was measured as a difference (d prime) between the rate of target (hit rate) to non-target (false alarm) responding, as well as secondary measures such as bias, reaction-time, variability of reaction-time, % omissions, and accuracy to respond in target location.
Results: AMP treatment affected numerous measures of 5C-CPT performance, including the primary outcome measure d prime which is a measure of the individual's discriminative power ($F(2,51) = 4.4$, $p < 0.05$), with post hoc analyses revealing that both 10 and 20 mg AMP improved performance ($p < 0.05$). AMP also affected secondary measures such as % omissions ($F(2,51) = 3.7$, $p < 0.05$), Hit Rate ($F(2,51) = 4.0$, $p < 0.05$), and accuracy ($F(2,51) = 6.0$, $p < 0.005$), while tending to affect reaction time ($F(2,51) = 2.5$, $p = 0.095$), the responsivity index of bias ($F(2,51) = 3.0$, $p = 0.057$), and variability of reaction time ($F(2,51) = 2.7$, $p = 0.08$). No effect of amphetamine was observed for False Alarm Rate ($F(2,51) < 1$, ns). Post hoc analyses revealed that 10 mg AMP did not affect reaction time or variable reaction time ($p > 0.1$). 10 mg AMP did however decrease % omissions ($p < 0.05$), increase hit rate ($p < 0.01$), increase responsivity index of bias ($p < 0.05$), and increased accuracy ($p < 0.05$). Treatment at 20 mg AMP reduced reaction time ($p < 0.05$), % omissions ($p < 0.05$), increased hit rate ($p < 0.05$), increased accuracy ($p < 0.1$), and reduced variability of reaction time ($p < 0.05$), without affecting responsivity index ($p > 0.1$). AMP group did not significantly interact with trial period for any measure, despite some evidence that d prime dropped over time in placebo-treated subjects, and increased over time in subjects treated with 20 mg AMP.
Conclusions: Amphetamine treatment significantly improved attentional performance of humans in the reverse-translated 5C-CPT as measured by d prime. Importantly, 20 mg AMP improved performance while not affecting bias, supporting a cognitive enhancing effect. AMP -induced improvement was driven by increased responses to targets without affecting non-target responses (response inhibition). AMP also sped reaction-time and improved accuracy, supporting a multi-faceted effect of improved overall 5C-CPT performance. These results indicate that it is possible to measure treatment-induced improvement in performance of healthy humans using the 5C-CPT, consistent with drug-induced improvements seen in healthy mice performing the 5C-CPT. These data support the translational relevance of the 5C-CPT. More importantly, given the clinical sensitivity of the 5C-CPT to deficits observed in bipolar mania and schizophrenia patients, this task could be used for future studies investigating pro-attentive treatments as well as the neurochemistry underlying attentional function.
Keywords: Response inhibition, 5C-CPT, Predictive validity, Translational research.
Disclosure: Dr. Young has received funding support from Omeros and Lundbeck, and consulting support from Amgen Ltd.

W63. Fearfulness Moderates the Link Between Childhood Social Withdrawal and Adolescent Reward Response

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Background: Consistent with findings of enhanced ventral striatal (VS) response to reward in clinically anxious youth, recent research suggests that socially withdrawn and inhibited children also show heightened VS response to reward. However, given that some children withdraw in social contexts because of social reticence and fearfulness whereas others withdraw as a result of preferred solitude or low sociability, the link between behavioral withdrawal and neural reward response may depend on these temperament traits, with only highly fearful children exhibiting heightened VS response to reward. Understanding how behavioral social withdrawal is related to neural reward response is clinically important, given that disrupted reward function is implicated in the pathophysiology of both clinical depression and social phobia.
Methods: Because social withdrawal has greater costs, such as loneliness, for boys relative to girls, the current study evaluated how childhood behavioral withdrawal and temperament may be associated with altered reward processing and history of affective disorders during the transition from adolescence to adulthood—a vulnerable period for psychiatric disorder—in a sample of 129 boys. At age 5, boys' mother-reported fearfulness and sociability was measured. Boys' teachers reported on the boys' withdrawn behavior in school at ages 6-10. At age 9/10, boys' social withdrawal was also assessed during a summer camp using camp counselor ratings and peer nominations. At age 20, boys' completed a widely-used fMRI monetary reward paradigm in a 3T scanner. Data were pre-processed and analyzed in SPM8 and corrected for Type 1 error using simulations in AFNI's AlphaSim program. At age 20, boys also completed a semi-structured interview assessing their psychiatric history. We evaluated whether the combination of fearfulness and behavioral social withdrawal predicted heightened VS response to reward at age 20. Using conjunction analysis in SPM8, we also tested whether altered VS function associated with social withdrawal and fearfulness during childhood predicted boys' diagnoses of depression and social phobia at age 20.
Results: As expected, greater social withdrawal during childhood was associated with heightened VS activation [205 voxels, 2, 14, 1, $t = 4.35$] when anticipating rewards at age 20. Fearfulness moderated this effect to indicate that childhood social withdrawal was related to heightened reward-related response in the ventral striatum at age 20

only for boys high on fearfulness [192 voxels, 0, 16, 1, t = 3.41], but not for those low on sociability. Altered VS response associated with social withdrawal and fearfulness also predicted greater likelihood to have a lifetime history of depression and social phobia at age 20, although the association between this cluster and these disorders was in opposite directions. Specifically, heightened VS response in this region [172 voxels, 4, 14, -1, t = 3.35] predicted social phobia whereas blunted VS response in this region [165 voxels, 6, 12, -1, t = 5.99] predicted clinical depression.
Conclusions: Our findings suggest that socially withdrawn children may be more sensitive to reward feedback and place greater value on rewards, perhaps due to being prone to high levels of hyper-vigilance and reticence in novel situations, which may enhance their anticipation of feedback. Disrupted reward function may increase psychiatric risk, as heightened response in the VS region associated with these childhood traits predicted social phobia and, reported for the first time in this study, low VS response in this region was related to depression. Fearful, withdrawn boys who are sensitive to rewards may be at heightened risk for developing social phobia, whereas fearful, withdrawn boys who are less motivated by rewards may be at greater risk for depression. Our findings are important as disrupted reward function has been implicated in various disorders, thus identification of associated processes can aid preventive intervention development. Interventions that target fearful, withdrawn children and use cognitive training to manipulate their response to potential reward may foster development of more adaptive self-regulation and reduce risk for psychopathology.
Keywords: Reward, Depression, Social Phobia, Withdrawal.
Disclosure: Nothing to Disclose.

W64. Effects of Tolcapone on Neurocognitive and Neurophysiological Measures in Healthy Adults

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Background: Neurocognitive deficits contribute strongly to functional disability in schizophrenia patients. Genetic studies have shown associations between specific genes and neurocognitive deficits in schizophrenia. SNP rs4680 of the catechol O-methyl transferase (COMT) gene results in fourfold variation in COMT enzyme activity resulting in lower forebrain dopamine levels and poor cognitive performance in Val/Val individuals compared to Met/Met individuals. Tolcapone, a reversible COMT inhibitor has been shown to improve working memory performance in Val/Val healthy subjects. Conceivably, candidate drugs might be first identified by positive effects on cognitive domains in sensitive subgroups of healthy subjects. We hypothesized that tolcapone will enhance neurocognitive task performance, measured by MATRICS Consensus Cognitive battery (MCCB) (a "gold standard" for pro-cognitive drug assessment in schizophrenia), in Val/Val healthy adults. Additionally, we will also examine tolcapone's effect on neurophysiological measures to confirm the neurobiological activity of the tolcapone dose, and determine the anatomical basis for its actions.
Methods: Healthy adults, between the age of 18-35 years are screened for baseline measures, COMT genotype; effects of single dose of tolcapone (200 mg or placebo p.o.) on MCCB performance are tested in a double-blind, randomized, counterbalanced, crossover design. Participants complete two test days separated by one week. The main effect of tolcapone on MCCB are analyzed using repeated measures ANOVA with tolcapone dose and MCCB domains as within subject factor and genotype or sex as between subject factor.
Results: 12 subjects (2 Met/Met and 10 Val/Val) have completed testing to date. Participants were healthy young (23.41 ± 5 yrs), educated (14.2 ± 1.5 yrs), men (83.3%) with an intelligence quotient (IQ) of 104 ± 11. Overall, tolcapone was well tolerated. A significant transient elevation in the liver enzyme, alanine transaminase (ALT; $p < 0.05$) was observed on follow-up liver function tests, however, these increased levels remained within normal limits and did not require clinical intervention. All participants showed mild elevations in blood pressure (mean increase systolic BP = 2 pts; effect size (d) = 0.3) and reported feeling calm (d = 0.4) on Symptom Rating Scale with tolcapone in a time-dependent manner. Collectively, these findings indicate that 200 mg of tolcapone was biologically active and well-tolerated. Tolcapone significantly improved performance on a verbal fluency task ($F = 6.4$, df (1,11), $p < 0.05$); in the current sample (n = 2 Met/Met), we detected no significant interactions of tolcapone x genotype. Tolcapone had no effect on each of 7 MCCB cognitive domains or composite scores.
Conclusions: Our preliminary findings suggest that tolcapone improved verbal fluency task performance in healthy adults. Similar findings have been reported by other groups. Testing is ongoing, and a complete analysis of tolcapone and COMT genotype effects on other cognitive domains and neurophysiological measures (prepulse inhibition, 5 Choice-Continuous Performance Test and No-Go anteriorization) will be reported.
Keywords: neurocognition, tolcapone, COMT gene, SNP rs4680.
Disclosure: Nothing to Disclose.

W65. Brain and Behavioral Evidence for Altered Social Learning Mechanisms Among Women with Assault-related Posttraumatic Stress Disorder

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Background: Current neurocircuitry models of PTSD focus on the neural mechanisms that mediate hypervigilance for threat and fear inhibition/extinction learning. Less focus has been directed towards explaining social deficits and heightened risk of revictimization observed among individuals with PTSD related to physical or sexual assault. Notably, leading neurocircuitry models of PTSD can neither predict nor explain the heightened risk of revictimization

and social deficits observed among this population. The purpose of the present study was to foster more comprehensive theoretical models of PTSD by testing the hypothesis that assault-related PTSD is associated with behavioral impairments in a social trust and reciprocity task and corresponding alterations in the neural encoding of social learning mechanisms.
Methods: Adult women with assault-related PTSD (n = 25) and control women (n = 15) completed a multi-trial trust game outside of the MRI scanner. A subset of these participants (15 with PTSD and 14 controls) also completed a social and non-social reinforcement learning task during 3T fMRI. Computational models of reinforcement learning were fit to the brain and behavioral data. Trust investments and modeled cognitive learning mechanisms during the trust game were compared between groups. Brain regions that encoded the computationally modeled parameters of value expectation, prediction error, and volatility (i.e., uncertainty) were defined and compared between groups.
Results: The PTSD group demonstrated slower learning rates during the trust game and social prediction errors had a lesser impact on subsequent investment decisions. PTSD was also associated with widespread alterations in the neural encoding of social learning mechanisms. In particular, PTSD was associated with greater encoding of uncertainty in the left hippocampus, less encoding of value expectation in the right amygdala, hippocampus, left temporoparietal junction, and medial PFC, and greater encoding of social prediction errors in the left temporoparietal junction. Degree of value expectation encoding in the temporoparietal junction mediated the behavioral impairments observed on the trust game.
Conclusions: These data suggest mechanisms of PTSD-related deficits in social functioning and heightened risk for re-victimization in assault victims. Leading neurocircuitry models posit hyperactive anterior insula and amygdala and a hypoactive hippocampus as key neural mechanisms of PTSD symptomology. The current results demonstrate unique alterations in these regions and their encoding of social learning mechanisms that are only consistent with neurocircuitry models if context (social vs emotional) is considered a moderating variable. Further, the current results demonstrate altered neural encoding in a region commonly implicated in theory mind (i.e., TPJ) that is not canonically linked with PTSD nor predicted by neurocircuitry models of PTSD.
Keywords: PTSD, fMRI, social learning.
Disclosure: Nothing to Disclose.

W66. Perception under Uncertainty and Its Relationship to Psychosis Predisposition

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Background: Bayesian models of perception and inference have been increasingly used in psychiatry research as a framework for understanding a variety of psychotic symptoms, including hallucinations and delusions. These models postulate that the brain represents context-dependent expectancies as well as the uncertainty or variance associated with these expectancies, both of which shape subjective perception and decision making. Abnormal representation of the uncertainty associated with expectancies may lead to a distorted influence of expectancy on perception, which has been suggested to underlie hallucinations and other psychotic symptoms. Here, we studied whether predisposition to psychosis in the general population is associated with the degree to which uncertainty affects the subjective perception of temporal intervals.
Methods: We studied a group of healthy participants (n = 31) using a Variable Context Tone Reproduction (VCTR) task in which participants listened to a series of pure tones (1000 Hz) and reproduced the duration of 700 ms probe tones preceded by 2-4 context tones. Series of context tones differed in both mean tone duration (context mean: long, intermediate, or short) and variance in tone duration (context variance: high, low). Participants also completed two validated scales that measure the predisposition of healthy individuals to experience hallucination- or psychosis-like phenomena: the Launay–Slade Hallucination Scale (LSHS) and the Community Assessment of Psychic Experiences (CAPE). We tested the degree to which context mean and variance influenced probe interval reproduction using hierarchical linear regression and model fitting with reinforcement-learning models assuming either fixed learning rates or with different learning rates for different levels of uncertainty.
Results: The mean duration of context tones influenced the perceived duration of probe tones. The direction of this influence was consistent within participants but differed across participants. Regardless of the direction of influence, context mean had a stronger influence on perceived duration when the contexts were low-variance as compared to the high-variance contexts (interaction of context variance by absolute context mean: $t(30) = -3.1$, $p = 0.004$; Levene's test of signed context mean effect: $F(30) = 6.9$, $p = 0.01$). Model-based analyses showed that best-fitting learning rates for low-variance vs. high-variance contexts significantly differed ($t(30) = 3.6$, $p = .001$) and that models with learning rates that adapted to context variance captured the data better than a model with a fixed learning rate. These results indicate that subjective perception of time depends on both mean duration and variance of the context, compatible with a sensory learning process that is sensitive to contextual uncertainty. Finally, the magnitude of the interaction of context variance by context mean correlated positively with propensity for hallucination-like phenomena and other subclinical positive symptoms (CAPE-PS frequency, $r = 0.46$, $p = 0.010$; LSHS, $r = 0.44$, $p = 0.016$), even after controlling for other subclinical symptoms (LSHS: $B = 0.32$, $p = 0.040$; CAPE-PS frequency: $B = 0.30$, $p = 0.062$), suggesting that the perceptual modulation by contextual variance may be relevant to psychosis propensity.
Conclusions: These data encourage the use of Bayesian models of perception whereby our experience of the world is biased by our knowledge about the statistical regularities (mean and variance) of the environment. Individuals perceived tones of equal duration differently depending on the mean duration of the preceding (context) tones;

further, the effects of context mean on perception were weaker if expectancies generated by the context were more uncertain (i.e., high-variance contexts influenced perception less than did low-variance contexts). Finally, consistent with Bayesian accounts of psychosis, healthy individuals with propensity for psychosis-like experiences tended to have abnormal effects of context variance on subjective perception. Together, our results suggest that incorporation of contextual uncertainty into subjective perception may play an important role in normal perception as well as in perceptual and inferential abnormalities in psychosis.
Keywords: Perception, Bayesian inference, Auditory hallucinations, Psychosis.
Disclosure: Nothing to Disclose.

W67. A Multidimensional Approach to Studying Responses to a Methamphetamine-associated Contextual Cue in Healthy, Non-dependent Humans

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Background: Conditioning, the process by which a cue becomes associated with drug through repeated pairings, is the focal point of many theories of addiction, and is believed to contribute to the acquisition, maintenance, and relapse to problematic drug use. Drug-related cues promote drug craving, seeking, and consumption, even after long periods of drug abstinence. Although cues are known to play a crucial role in the cycle of addiction, few studies have examined the acquisition process and the behavioral features of conditioned drug responses in humans. Drug-related cues have been studied in established drug users whose responses developed after many years of drug experience, but the process of acquisition has not been examined. Therefore, we have developed a novel human drug conditioning paradigm to determine the acquisition of responses to a cue paired with a typical drug of abuse (i.e. methamphetamine) in humans. We employed a multidimensional approach to determine the various ways in which the responses manifest, and we examined individual differences in conditioning.
Methods: In this study, healthy adults (ages 21-35; N = 90) participated in 6 sessions: a pre-test session, 4 conditioning sessions, and a post-test session. At the pre-test session, we assessed pre-conditioning responses to two audio-visual study cues using the following measures: behavioral preference, self-reported subjective "liking", emotional reactivity (assessed via facial electromyography of the corrugator and zygomatic muscles) and attentional bias (measured using electrooculography during a modified dot probe task). Participants then attended four conditioning sessions; two each with drug (20 mg methamphetamine; MA) and placebo, administered under double-blind conditions in alternating order. The two cues presented at pre-test were displayed on a computer screen for 30 min during peak drug effect, one during the MA sessions and the other during the placebo sessions. Cues consisted of a background screen and soundtrack present while the participant completed simple computer tasks. Following the conditioning sessions, participants completed a post-test session similar to the pre-test session, in which we assessed behavioral preference, self-reported liking, emotional reactivity, and attentional bias towards the cues. Conditioning was quantified as the change in conditioning measures from pre- to post-test.
Results: Conditioned responses to the MA-paired cue were observed after the pairing sessions. There were increases on measures of behavioral preference, emotional reactivity (corrugator and zygomatic reactivity) and attentional bias, for the MA-paired, compared to the placebo-paired stimuli. Self-reported ratings of liking the cues were unaffected. Some individual differences were apparent: positive self-reported subjective drug effects (i.e. ratings of "liking" drug effects and "wanting more" drug) predicted the greatest increase in attentional bias. Future analysis will further explore individual differences in conditioning and potential relationship between other risk factors for problematic drug use (i.e. impulsivity).
Conclusions: This study demonstrates that conditioning develops between drug effects and environmental stimuli in humans. Notably, this effect developed after only two pairings of a moderate dose of a drug, in nondependent individuals. As such, it may provide an important indicator of risk for developing drug use problems. This research addresses an important gap in knowledge about drug conditioning in humans. Future studies may identify individuals at risk for cue-elicited drug seeking and consumption, and may aid efforts to prevent or attenuate cue-facilitated drug seeking and relapse.
Keywords: conditioning, methamphetamine, attentional bias, emotional reactivity.
Disclosure: Nothing to Disclose.

W68. Working Memory Capacity Promotes Optimal Emotion Perception

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Background: Emotion Perception, inferring the emotional state of another person, is a frequent judgment made under perceptual uncertainty (e.g., a scowling facial expression can indicate anger or concentration) and behavioral risk (e.g., incorrect judgment can be costly to the perceiver). Working memory capacity (WMC), the ability to maintain controlled processing, is an important component of many decisions. The present study aims to examine the influence of WMC on an "anger" detection task in which "angry" and "not angry" categories shared morphed facial scowl intensities and correct and incorrect responses earned and lost points, respectively.
Methods: Thirty-seven healthy control participants were recruited to the Center for Anxiety and Traumatic Stress Disorders at Massachusetts General Hospital by local hospital and media advertising. Participants completed the Run Letter Span task (Broadway & Engle, 2010), an automated running memory span task (Unsworth, Heitz, Schrock, & Engle, 2005), in order to assess WMC. Participants then completed an "anger" detection task under perceptual uncertainty ("angry" and "not angry"

categories shared morphed facial scowl intensities) and risk (correct and incorrect responses earned and lost points, respectively). Participants attempted to earn as many points as they could, and a slight bias to respond "not angry" would maximize points.
Results: Participants (age $M = 39.5 \pm 16.01$ [SD] years, 48.6% women) with higher working memory capacity were better able to adjust their response bias to accommodate their perceptual sensitivity (ability to discriminate the categories) than those with lower working memory capacity ($P < .037$, $Rho = .35$). Working memory capacity did not predict bias ($P > .09$), sensitivity ($P > .22$), or overall accuracy ($r = 0.24$, $P > .14$).
Conclusions: Response bias and sensitivity are not independent in perceivers—under biased conditions, achieving optimal bias requires accounting for poor sensitivity. Our results suggest that working memory capacity enables effective judgments about the emotional state of others by contributing to a perceiver's ability to adjust their response bias to account for their level of perceptual sensitivity.
Keywords: Working Memory Capacity, Emotion Perception, Decision Making, Signal Detection Theory.
Disclosure: Nothing to Disclose.

W69. Slow Information Processing and Thalamo-Cortical Dysconnectivity are Associated in Clinical High Risk Subjects who Convert to Psychosis: Findings from the North American Prodrome Longitudinal Studies

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Background: The study of individuals at Clinical High Risk (CHR) for psychosis has become an increasingly important area of investigation. Using clinical and demographic criteria, it is now possible to identify individuals with a 35% chance of developing a psychotic illness within 2.5 years. The use of biomarkers in CHR research has enabled enhanced prediction of psychosis and a greater understanding of the possible mechanisms by which psychosis emerges. The development of reliable, mechanistically-linked biomarkers that can easily be used in the clinical setting may enable individualized treatments based on biomarker profiles. In the North American Prodrome Longitudinal Studies (NAPLS) consortium we have identified both electrophysiological and neuroimaging paradigms that predict psychotic conversion with greater accuracy when combined with the clinical criteria. Specifically, the latency of the human startle response, a measure of speed of information processing that can be assessed in a simple electrophysiological paradigm, is greater in CHR individuals who later develop psychosis. Similarly, baseline resting-state thalamo-cortical dysconnectivity, measured with fMRI, identifies CHR subjects who later converted to psychosis.
Methods: In the present study we identified 106 CHR individuals from the 8 site NAPLS consortium who had both startle and fMRI data from baseline assessment. The startle paradigm included acoustic startle pulse alone stimuli (115dB white noise). The latency of the electromyographic (EMG) responses was recorded at the obicularis oculi muscle. Whole-brain thalamic functional connectivity maps were generated using individual subjects' anatomically defined thalamic seeds, measured using resting-state functional MRI.
Results: Greater startle latency was significantly correlated ($r = -23$, $p < 0.02$) with thalamic hypo-connectivity in CHR individuals at baseline assessments. The correlations were larger in the small sample ($N = 9$) who converted to psychosis ($r = -0.39$), accounting for 16% of the variance.
Conclusions: It is likely that similar underlying processes including microglial activation, inflammation and reduced synaptic plasticity lead to loss of neuropil and patterns of slowed processing and dysconnectivity. Future studies will explore these hypothesized mechanisms further in order to isolate those systems that should be targeted with selective intervention. Further development of biomarkers for reliable use in the clinic will contribute to more precise diagnosis and treatment in this vulnerable clinical high risk population.
Keywords: prodrome, psychosis, startle, resting state.
Disclosure: Nothing to Disclose.

W70. Anatomical Properties of Emotion Arousal Regions are Associated with Early Adverse Life Events and Vary Based on Sex

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Background: Structural and function neuroimaging studies have shown that alterations in regions of emotional arousal including have been associated with early adverse life events. The architecture of large-scale anatomical brain networks can be described by quantifying local measures of centrality that index a brain region's contribution to the network's structural integrity and information flow (Rubinov & Sporns, NeuroImage, 2010). The simplest measure of centrality is degree, the number of regions connected to a region. Regions with high degree are considered essential for facilitating functional integration. The ability of a region to propagate information across a network of regions is referred to as local efficiency. We hypothesized that differences in the degree and clustering coefficients of emotional arousal network regions would be related to reports of early adverse life events in healthy controls.
Methods: Using structural and diffusion tensor imaging, gray and white matter in the brain were measured in 90 healthy subjects, 46 males and 44 females. Segmentation and regional parcellation of each individuals brain into 165 regions was performed using Freesurfer on the USC Laboratory of Neuroimaging pipeline based on Destrieux and Harvard-Oxford Atlases. Deterministic tractography using the Runge-Kutta algorithm was performed using TrackVis and provided a measure of relative fiber density

between regions (Irimia et al., NeuroImage, 2012). Anatomical network metrics were generated using the Brain Connectivity Toolbox. The Early Trauma Inventory (ETI) was used to access history of childhood traumatic and adverse life events in four domains: general trauma and physical, emotional, or sexual abuse (Bremner et al., 2007, J Nerv Ment Dis). Controlling for the main effects of age and sex, the general linear model was applied to examine the association between total scores on the ETI with degree and clustering coefficients of regions comprising emotional arousal regions including the amygdala, dorsal anterior cingulate cortex (ACC) (pregenual ACC, anterior midcingulate), and subgenual ACC and medial frontal gyrus. We also include an interaction term to determine whether the interaction between ETI and topology of the regions of interest were moderated by sex. Significant interaction effects were examined using partial correlations by sex controlling for age. Significance was set at $p < .05$ uncorrected.

Results: No differences in ETI scores was observed between males and females [mean total score = 4.36 (SD = 4.107)]. Males were significantly older than females in this sample ($t(88) = 3.21$, $p = .002$). Association between early adverse life events and degree of emotional arousal regions. Interaction effects were observed between sex and total ETI score with degree of right subgenual ACC($\beta = 0.25$, $p = .019$) and the left pACC($\beta = .31$, $p = .03$). After controlling for age, females($r(41) = -.48$, $p = .001$) but not males ($r(43) = -.10$, $p = .53$) had large negative correlation between degree of the subgenual ACC and ETI total score. On the other hand, males ($r = .35$, $p = .02$) but not females ($r = -.16$, $p = .30$) showed strong positive association between degree of pACC connectivity and ETI. Across sex, ETI total score was positively associated with degree of left amygdala ($\beta = .25$,$p = .038$), and left ($\beta = .44$,$p = .016$) and right ($\beta = .41$,$p = .014$) middle frontal gyrus. Association between early adverse life events and local efficiency of emotional arousal regions. Significant interaction effects were observed for the right pACC ($\beta = .002$, $p = .01$) and the right anterior midcingulate cortex ($\beta = .003$, $p = .01$). For males $r(43) = .39$, $p = .008$ but not females ($r(41) = -.21$, $p = .18$) ETI total score was positively associated with local efficiency of the pACC. For females($r = -.31$, $p = .04$) but not males ($r = .21$, $p = .18$) local efficiency of the pACC was negatively correlated with ETI total score. Across sex, EALs were associated with local efficiency of right medial frontal gyrus ($\beta = -.003$, $p = .003$) and right subgenual cingulate ($\beta = .003$, $p = .03$).

Conclusions: The network architecture of core emotional arousal network regions were associated with a history of early adverse life events. Findings indicate that exposure to early adverse life events affect not only the developing brain during childhood and adolescence but these alterations persist into adulthood as seen in this nonclinical sample of healthy men and women. The role of these changes in vulnerability to mental or physical illness is unknown.

Keywords: early life stress, brain, graph theory, emotion.

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W71. M100 Amplitude and Oscillatory Activity as Markers of Abnormal Response to Auditory Paired Click Stimuli in Psychosis

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Background: Auditory processing deficits measured through with EEG with the paired-click paradigm via event-related potentials (ERPs) at 50 and 100 milliseconds have been considered strong biomarkers (endophenotypes) in schizophrenia (SZ). Several studies have described similar, albeit less severe deficits in bipolar disorder (BD) with psychosis (BDP), including the large multicenter Bipolar Schizophrenia Network for Intermediate Phenotype (BSNIP), suggesting that this measure may be a broader marker of psychosis rather than schizophrenia alone. Analyses of oscillatory activity related to stimulus processing disclose both similar and unique abnormities. Although support for the conventional Kraepelinian differences between these two disorders is dwindling, the persistent differences in socio-occupational disability and life span warrant further investigation. In addition it is crucial to further investigate the (BD) without psychosis (BDNP) group as part of the bipolar spectrum. Our previous MEG studies in schizophrenia have provided evidence of hemispheric differences. Only one MEG study has examined bipolar disorder. We hypothesize that specific hemispheric differences in M50 and M100 amplitude will be seen among these groups by employing MEG source analysis. We further hypothesize that underlying oscillatory activity (alpha band) in part accounts for the differences in M50 and M100 amplitudes by group and may indicate specific network abnormalities among psychoses.

Methods: Twenty-two subjects with schizophrenia (SZ), seventeen with bipolar disorder with psychosis (BDP), twweve individuals with bipolar disorder without psychosis (BDNP), and twenty-two healthy controls (HC) were recruited. All patients were medicated. A paired click auditory sensory gating paradigm was presented with 3 ms duration clicks presented 500 ms apart with an intertrial interval of 10 seconds. MEG data were collected using the Elekta Neuromag 306 channel system. The sources generating the M50 and M100 responses were localized using a multidipole spatio-temporal modeling approach (CSST – Ranken et al. 2004). Time frequency analysis was performed using a modified Fieldtrip (http://fieldtrip.fcdonders.nl/) analysis pipeline. Time-frequency group differences and associations between M50 and M100 latency and age were examined.

Results: We reliably identified left and right STG sources during the M50 and M100 time window of response as well as left and right frontal sources. The pattern of reduced S1 amplitude responses in left STG in SZ was replicated in this study with the M100 peak amplitude showing a significant interaction of hemisphere by diagnosis by condition. In this analysis the SZ and BDP amplitudes were reduced relative to the BDNP and HC groups. To understand the link between oscillatory and evoked activity, we analyzed the

underlying oscillations associated with the M50 and M100 response using co-author Stephen et al (2013) time-frequency analysis. Percent signal change relative to baseline was reduced in SZ vs. HC in the alpha frequency band. Furthermore, BD revealed reduced percent signal change in the alpha band relative to HC. Interestingly, the HC group showed a significant correlation between alpha percent signal change and M50 amplitude ($r11 = 0.62$, $p = 0.04$), whereas the remaining patient groups did not. Significant differences between STG and frontal sources were not obtained in this sample, but the frontal peak latency was generally delayed relative to the STG M100 peak latency (left STG 126 ms vs. frontal 141 ms; $p = 0.1$).

Conclusions: These results suggest that evoked responses, at 100 ms in particular, and the underlying oscillatory activity differ by group and may both play a role in the pathophysiology of psychoses. The hemispheric effects were most prominent in SZ; the lack of significance in BD subjects may indicate either no hemispheric difference or a lack of power to detect any difference in the current sample. Our results also provide evidence that BDNP subjects respond similarly to the HC group. The differences in percent signal change in the alpha band are consistent with our previous study suggesting that alpha power is reduced in SZ relative to HC. However, in this case the BDP and BDNP subjects showed further reductions in alpha band power relative to SZ and HC. In contrast, the BSNIP study identified changes in theta band power. Limitations of this study include a sample size and not controlling for medication effects. These results provide additional evidence that MEG may help elucidate hemispheric and oscillatory changes across the psychosis spectrum. Future plans include increasing the sample size and investigating the implications on cognition and social functioning.

Keywords: psychosis, auditory processing, alpha, magentoencephalography.

Disclosure: Nothing to Disclose.

W72. Gray Matter Volumes in Young Adult Offspring from Families at Ultra-high Risk for Alcohol Dependence Through the Maternal Line: A Voxel Based Morphometry Study

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Background: There is an emerging literature suggesting that structural abnormalities exist in offspring from families selected to have multiple members with alcohol dependence. Structures previously identified by manual tracing techniques include the orbitofrontal cortex and amygdala, regions involved in emotional processing. Deficits in social cognition have been reported in alcoholic patients with a suggestion that these deficits may be linked to prefrontal cortex (PFC) dysfunction. It is possible that the prefrontal cortex may be more vulnerable to the neurotoxic effects of alcohol experienced from either personal or prenatal exposure, or both. Alternatively, familial risk for alcohol dependence may predispose individuals to PFC structural abnormalities. Voxel based morphometry (VBM) is well suited to uncovering whole brain differences between ultra high risk offspring and controls. While most studies have selected families through an alcohol dependent father, understanding the contribution that familial maternal alcoholism has on offspring that is independent of any fetal alcohol exposure effects that the offspring experience provides an opportunity to identify pathophysiologic mechanisms that may be unique to each. With this information targeted interventions could be developed. We hypothesized that decreased gray matter volumes might be seen in the high risk offspring relative to controls in cortical structures and include those associated with facial recognition and social cognition. Also, we hypothesized that comparison of high risk offspring with and without prenatal exposure would reveal new regions unique to exposure.

Methods: Structural MRI scans at 3.0 Tesla were obtained from 43 high risk offspring (Mean age $27.4 + 3.6$ years) and 45 low-risk controls (Mean age $24.5 + 4.1$ years). Substance use during pregnancy was obtained from mothers at a time when the young adult participants were studied as children as part of a longitudinal study. Within the high-risk group 16 offspring were exposed to alcohol and 25 were not providing an opportunity to determine which regions differed by familial risk and those due to alcohol exposure. Structural data preprocessing and analysis for this study was performed with the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) within the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2014a (Mathworks). Preprocessing steps in VBM8 toolbox involves bias correction, tissue segmentation, affine registration, normalization, and modulation. Finally, modulated images were smoothed with a full-width half-maximum kernel of 12 mm. Statistical analyses were performed on these smooth images. The resulting maps were thresholded with $p < 0.001$ with a cluster size of 50 voxels. Additionally, regional volumes were calculated using the MarsBaR ROI toolbox (http://marsbar.sourceforge.net) to compare the volume of the specified regions of interests (ROIs) which were further compared in SPSS (version 20).

Results: Whole brain analysis revealed clusters in the middle temporal gyrus, fusiform gyrus, and insula, regions associated with face processing in which high-risk offspring had lesser gray matter than low-risk controls. Also, found were areas of reduced gray matter in the uncus, cuneus, precuneous, claustrum, and caudate. Whole brain analysis was performed within the high risk group to assess the effect of prenatal alcohol exposure on gray matter volumes. In this comparison, clusters were identified within the middle frontal, and middle temporal gyri along with the precuneus and anterior cingulate in which exposed offspring had reduced gray matter compared to those that were not exposed. One area showed greater gray matter volume in the exposed offspring, the culmen portion of the right anterior lobe of cerebellum. Region of interest analysis revealed four areas associated with facial processing with lesser gray matter in association with familial risk: the fusiform gyrus ($p = 0.001$), middle temporal gyrus ($p = 0.024$), insula ($p = 0.042$) in the left hemisphere and the orbitofrontal cortex in the right hemisphere (0.040). Analyses using prenatal exposure to alcohol or cigarettes continued to show risk group differences as did analyses in

which presence of SUD before the scans was used as a covariate. Correlational analysis between these regions shows highly related structural connectivity with all intercorrelations significant at <0.001.
Conclusions: The fusiform gyrus, middle temporal gyrus, insula and orbitofrontal cortex have previously been linked to facial affect perception and social cognition. The present results indicate lesser gray matter volumes in these regions in individuals at ultra high risk for developing alcohol dependence and other substance use disorders. Moreover, the results suggest that the neural underpinnings of social cognitive impairment may be present before these individuals' development substance use disorders.
Keywords: alcohol dependence, familial risk, social cognition, VBM.
Disclosure: Nothing to Disclose.

W73. Psychosis Biotypes Account for Variations in Neural Synchrony During Cognitive Control: Findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes

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Background: Schizophrenia (SZ) and psychotic bipolar disorder (BDP) may have distinct and shared neurophysiological indicators of disease risk, although a psychosis continuum model accounts best for neurobiological data when groups are defined by DSM diagnoses. Previous B-SNIP data, however, document three distinct psychosis Biotypes with unique neurobiological features not accounted for by a simple continuum of severity model. Here, we demonstrate an additional unique feature of the psychosis Biotypes. Strength and distribution of neural synchrony under variations in cognitive control are purportedly critically related to functional deviations associated with psychosis. Deviations in these neurobiological features are best captured by Biotype designations but are not discriminating features for DSM psychosis categories.
Methods: Participants included healthy individuals (HC; $N=58$) and those with schizophrenia (SZ; $N=43$) and bipolar disorder with psychosis (BDP; $N=55$) from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) sample. Participants completed blocked pro- and anti-saccade tasks while 64-sensor electroencephalography (EEG) data was gathered. These data were not included in Biotype creation. Trials consisted of checkerboards in central and both peripheral visual fields, followed by brightening of one peripheral checkerboard (cue) after 5 sec. The central checkerboard flickered at 15Hz. The degree of ssVEP (15Hz) synchronization between the 2016 sensor pairs was assessed using intersensor phase coherence (ISC). To use ISC data from every sensor pair and thus to most accurately and comprehensively capture the shared variance in the spatial topographies of distributed synchronization of neural responses across time, data reduction using spatial principal components analysis (PCA) was performed. Further analyses included only sensor pairs with ISC values in 99th percentile (20 pairs each). Single trial power (STP) and intertrial phase coherence (ITC) for these sensors were also analyzed to more completely capture group and task differences in the resulting neural synchrony patterns.
Results: There were three significant components: (1) transmedial occipital connections (limited to extended visual cortex); (2) fronto-parietal to parieto-occipital; and (3) prefrontal cortex (PFC) to occipital. Virtual sensors for each PCA component indicate greater ISC across time during anti-saccade trials for HC, each component following a temporal pattern of ISC increasing from baseline in the 1000ms after stimulus presentation, plateauing throughout the entrainment period, then returning to baseline after cue presentation. The diagnosis-based outcomes reveal increased absolute ISC as well as greater ISC modulation for Anti in SZ and BDP across all components, compared to HC. These differences from HC, however, overlapped between DSM psychosis groups, with little indication of neurobiological uniqueness of SZ and BDP. There was, however, a tendency for BDP to have greater ISC than SZ in fronto-parietal to parieto-occipital connections. The Biotype-based outcomes reveal a number of differences: (1) For local occipital connections, B1 and B2, the most cognitively compromised subgroups, show increased ISC compared to HC, with particularly accentuated ISC modulation for Anti-trials. For B1, the most neurobiologically compromised subgroup, this ISC modulation was accompanied by decreased ITC for Pro-trials. For B2, the subgroup with accentuated sensorimotor reactivity, this modulation co-occurred with increased STP and ITC on Anti-trials across occipital cortex. For B3, the subgroup most like HC on all other measures, there were no ISC differences from HC. (2) For fronto-parietal to parieto-occipital connections, all groups differed on ISC and degree of ISC modulation on Anti-trials, within $HC<B3<B2<B1$. Notably, B1 also had the lowest STP, indicating lower levels of neural responding. (3) For PFC-occipital connections, all groups including HC show similarly low ISC values for Pro-trials. The Biotypes, however, had significantly enhanced ISC compared to HC on Anti-trials. B1 had the most extreme ISC increase on Anti-trials, which was accompanied by dramatically lower STP and ITC in PFC. B2 had less enhanced ISC than B1, but this enhancement was accompanied by increased occipital STP and ITC. B3 had the least extreme ISC enhancement on Anti-trials though still more than HC.
Conclusions: Our findings using DSM diagnosis suggest absolute levels of synchrony between fronto-parietal and parieto-occipital regions may differ slightly between SZ and BP, though these groups exhibited statistically equivalent task-related differences. Proband classification using the Biotypes, however, revealed subgroup differences in overall ISC and task-related ISC modulation in all network-structures examined. These findings were also consistent with other data on Biotype differences using other EEG and structural and functional neuroimaging measures. The relationship between ISC and underlying STP and ITC also differs between HC and each of the Biotype groups. These findings provide further support for the classification of psychotic disorders by way of endophenotypic Biotypes in

general and the Biotypes described by previous B-SNIP publications in particular.
Keywords: schizophrenia, bipolar disorder, endophenotype, EEG.
Disclosure: Nothing to Disclose.

W74. Aggression in Early Psychosis is Associated with Impairments in Prefrontally-mediated Cognitive Reappraisal of Emotion

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Background: Impairments in prefrontally-mediated cognitive control are a core feature of psychotic illness and linked to aggressive behavior. However, the specific clinical, cognitive and neural mechanisms underlying aggression in early psychosis are poorly understood, precluding the development of targeted treatments or identification of individuals at greatest risk for aggressive behavior. Using fMRI and an established measure of cognitive reappraisal (Ochsner, 2002), we examined relationships between aggression and prefrontal network functioning during reappraisal of negative emotional stimuli in early psychosis individuals with aggression (Agg-EP) and without (NonAgg-EP) and healthy controls (HC). We predicted that Agg-EPs will report reduced ability to reappraise negative affect (DECREASE:Negative-LOOK:Negative) in comparison to both NonAgg-EPs and HCs. Further, relative to NonAgg-EPs and HCs, Agg-EPs will show increased activity in amygdala under conditions of high emotional reactivity (LOOK: Negative trials) and reduced activation in prefrontal regions during reappraisal (DECREASE:Negative-LOOK:Negative).
Methods: HC ($n=7$) and EP ($n=14$: Agg $n=8$ and NonAgg $=6$) participants from the UC Davis Early Psychosis programs were identified using the Structured Clinical Interview for DSM-IV (SCID-I/P). Aggression status was based upon a reported history of aggression towards self and/or others ascertained via clinical chart review and collateral information from current clinicians. Participants completed the Reappraisal task during fMRI on a 3 Tesla scanner. Differences between groups on self-report ratings of negative affect were examined with ANOVA using SPSS 21. Functional MRI data were processed using SPM8 and focused on between-groups contrasts of the high emotional reactivity (LOOK: Negative trials-Baseline) and reappraisal conditions (DECREASE:Negative-LOOK:Negative). Whole-brain and region of interest (ROI) analyses for the DLPFC and amygdala were performed.
Results: Consistent with hypotheses, HCs showed the greatest ability to decrease self-reported negative affect via reappraisal compared to both Agg-EP ($p=.002$) and NonAgg-EPP ($p=.03$). NonAgg-EP individuals showed a trend toward improved reappraisal of negative affect when compared to Agg-EP individuals ($p=.09$; Cohen's $d=.74$). Preliminary whole brain analyses revealed that HCs and NonAgg-EPs demonstrated significantly greater PFC activation during the reappraisal condition compared to Agg-EPs, with no significant differences observed between HCs and NonAgg-EPs. In the ROI analysis, Agg-EPs demonstrated a pattern of increased amygdala under conditions of high emotional reactivity in comparison to NonAgg-EPs (Cohen's $d=.91$). Furthermore, Agg-EPs did not increase DLPFC activity in response to increased cognitive control associated with reappraisal demands when compared to NonAgg-EPs ($p=0.05$, Cohen's $d=2.98$).
Conclusions: Preliminary findings indicate that aggressive behavior in early psychosis is associated with decreased ability to engage prefrontally-mediated cognitive control mechanisms that enable the cognitive reappraisal of emotional information to decrease negative affect. Given that reappraisal can be improved with training and represents a core component of cognitive-behavioral interventions, which are effective treatments for individuals with psychosis, targeted intervention to improve reappraisal skills in EP individuals could serve to reduce aggressive behaviors and improve functional outcomes. Data from an expanded sample of subjects will be presented.
Keywords: early psychosis, aggression, reappraisal.
Disclosure: Nothing to Disclose.

W75. ABCB1 Genetic Variants and Neurocognitive Function Predict Antidepressant Outcomes

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Background: The ABCB1 gene encodes P-glycoprotein (P-gp) that controls efflux of substrate agents out of brain across the Blood Brain Barrier. While many antidepressants are P-gp substrates, they differ in their effects on the P-gp pump. Sertraline has been thought to inhibit P-gp; escitalopram is neutral; and venlafaxine is a stimulator. At the patient level, cognitive impairment distinguishes some but not all patients and is associated with poorer treatment outcome. In a large pragmatic trial, we tested the effects of variants in 10 MDR-1 SNP's on remission achieved with treatment with escitalopram, sertraline or venlafaxine XR. We also explored the combined effects of ABCB1 genetic variation and degree of cognitive impairment on remission.
Methods: We genotyped 10 ABCB1 SNPs in 683 patients with major depressive disorder (MDD) treated for at least 2 weeks with escitalopram, sertraline, or venlafaxine-extended release (XR) in a large randomized, prospective, pragmatic trial: iSPOT-D. Of these 683 patients, 84% completed 8 weeks of treatment. Outcome endpoints were remission (QIDS16-SR $<=5$) and side effects (FIBSER). Based on our previously established method, patients were stratified by performance on tests of general and emotional cognition was assessed with a computerized battery.
Results: A significant treatment by genotype was observed for rs10245483 ($p<.0007$), aFor the functional SNP upstream from ABCB1. Common homozygotes were more likely to remit, with fewer side effects, escitalopram and sertraline with significantly fewer side effects observed for escitalopram. By contrast, minor allele carriers were more likely to remit, with fewer side effects, on venlafaxine-XR. Reflecting a double dissociation, minor allele carriers had more side effects if treated with escitalopram and sertraline and not venlafaxine-XR. Cognitively impaired patients who

were minor allele carriers for rs2214102 remitted more often than did others, particularly on sertraline.
Conclusions: Our results suggest that ABCB1 polymorphisms rs10245483 and rs2214102 have utility for helping select antidepressants likely to assist in symptom relief without escalating side effects and in boosting the chances of remission in a specific subset of cognitively impaired patients.
Keywords: antidepressant, ABCB gene, neurocognition, biomarker.
Disclosure: A. Schatzberg: BrainCells, CeNeRx, CNS Response, Eli Lilly, Forest Labs, Genetech, Gilead, GSK, Jazz, Lundbeck, Merck,Neuronetics, Novadel, Novartis, Pathway Diagnostics, Pfizer, PharmaNeuroBoost, Quintiles, Sanofi-Aventis, Sunovion, Synosia, Takeda, Xytis and Wyeth. Dr. Schatzberg has equity in Amnestix, BrainCells, CeNeRx, Corcept (co-founder), Delpor, Forest, Merck, Neurocrine, Novadel, Pfizer, PharaNeuroBoost, Somaxon, Synosis, and Titan. He is a named inventor on pharmacogenetic use patents on glucocorticoid antagonists and on prediction of antidepressant response. Dr. Schatzberg has also received speaking fees from Merck, GlaxoSmithKline and Roche C DeBattista: Research funding from Brain Resource, Takeda, CNS response, St Jude Medical, Aztra Zeneca, and Roche. He has served as a consultant to Genentech and Pfizer A. Etkin: Research funding from Brain Resource. L. Williams: Consultant fees from Brain Resource.

W76. Identification of a Common Neural Circuit Disruption in Executive Function Across Psychiatric Disorders

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Background: Historically, diagnostic categories have been conceptualized as discrete phenotypes. Investigation into related executive dysfunction has thus proceeded by comparing individual diagnostic groups to healthy control participants. This heuristic has provided compelling, albeit parallel evidence of prevalent executive dysfunction in discrete disorders observed in both brain network activation and behavior. Meanwhile, limited findings exist on the relative patterns of impairment across disorders. Transdiagnostic meta-analysis of the wealth of accumulated findings could productively highlight not only unique, but possibly even more importantly—common impairments in cognitive control networks.
Methods: One hundred, eighty-six articles published prior to August 2014 including 6,619 participants varying in age from adolescence to late life (median = 32 years) were submitted to meta-analysis. Patients (N = 3,940) across a range of Axis I diagnoses (bipolar, major depression, dysthymia, OCD, PTSD, substance abuse/dependence, schizophrenia, schizoaffective, first-episode psychosis) and 2,679 controls were included. Articles selected for inclusion focused on executive function tasks during functional imaging (fMRI or PET) and reported significant whole-brain, voxel-wise group differences (patient > control/control > patient) with corresponding peak coordinates in stereotactic space. Experimental paradigms primarily included n-back, AX/CPT, Stroop, Go/No-Go, and task switching. The Activation Likelihood Estimation (ALE) method with a family-wise error correction for multiple comparisons was implemented for analysis. To allow for adequate power, patients were aggregated into superordinate categories of psychotic (96 studies) or non-psychotic (90 studies) disorders. Unique and common executive functioning impairments in non-psychotic and psychotic disorders were examined with omnibus analysis of group (psychotic/non-psychotic) x hyper/hyporeactivity relative to controls (patient more/less than control and vice versa). Significant effects were followed up with conjunction analysis and separate main group effects.
Results: The most robust findings were revealed in deficits common to both psychotic and non-psychotic patients, specifically hypoactivation of right anterior insula and dorsal anterior cingulate (dACC). Analyses also revealed a unique pattern of hypoactivation in psychotic patients relative to controls in a key cognitive control region—dorsolateral prefrontal cortex (dlPFC). Though not as pronounced as the dlPFC signature in psychotic patients, non-psychotic patients relative to controls uniquely recruited less basal ganglia (putamen) activation to deploy cognitive resources. Additional analyses will examine differences in network and regional connectivity.
Conclusions: While psychotic and non-psychotic disorders showed distinct deficits in dlPFC and basal ganglia activation respectively during cognitive challenge, both groups showed a clear, common deficit in the failure to recruit dACC and right anterior insula—central regions in the salience network. In a recent transdiagnostic meta-analysis of regional gray matter volume, Etkin and colleagues (Goodkind et al., in press) observed atrophy across non-psychotic and psychotic patients alike in the same nodes of the salience network (i.e., bilateral insula and dACC). Linking the variation in structural integrity to behavior, Etkin and colleagues further demonstrated that even among healthy participants, lower gray matter volume in these two regions predicted performance decrements in executive function tasks. Taken together with the current findings of impaired functional activation in dACC and insula during a range of executive function tasks—across Axis I disorders—the salience network is strongly implicated as a common pathway to cognitive dyscontrol in psychopathology and possibly as a powerful common target for therapeutic intervention.
Keywords: neuroimaging, executive function, depression, cognition.
Disclosure: Nothing to Disclose.

W77. Psychosis Severity and Cortical Response to Irrelevant Sounds and Irrelevant Visual Stimuli

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Background: While hallucinations are among the more responsive psychosis symptoms to antipsychotic medication, complete resolution is more rare than common, and in

about one-fourth of cases, treatment is ineffective. Improved understanding of neural system dysfunction associated with psychosis symptoms, and specifically hallucinations, may guide understanding of differential treatment response and new treatment development. Sensory system dysfunction in schizophrenia and related psychotic disorders has been hypothesized due to hallucinations. Normally, there is robust top down attention-mediated modulation of sensory cortex responsiveness, a mechanism for filtering out irrelevant stimuli. This study aims to assess the integrity of top down control over sensory cortex response in individuals with psychotic disorders and to evaluate its association with dimensions of hallucination severity and other clinical features.
Methods: Psychosis (schizophrenia, schizoaffective, psychotic bipolar) patients were recruited and rated for illness severity using the Positive and Negative Syndrome Scales (PANSS). Auditory hallucination severity was assessed with the Psychotic Symptom Rating Scales (PSYRATS), and severity of hallucinations in other sensory modalities was assessed with the Chicago Hallucination Assessment Tool (CHAT), which adapts the PSYRATS items for rating hallucinations in all sensory modalities at both the present time and the past/worst time. Demographically-matched healthy individuals were also recruited. All participants were given tests of general cognitive function (Brief Assessment of Cognition in Schizophrenia [BACS]), and underwent fMRI studies while performing an attention task with irrelevant stimuli added. For the task, they were to press a button each time they saw an X in a group of 6 letters onscreen for 300ms (followed by 700ms of blank screen), with a new letter circle every 1s. X was present in 50% of trials. This task had three difficulty levels: easy, medium, and hard, and was presented in blocks of each difficulty level. Irrelevant stimuli were presented continuously during some blocks - either irrelevant sounds (trains of white noise bursts) or visual motion at the periphery of the screen. Increasing difficulty levels of the attention task are normally associated with decreasing levels of sensory cortex responsiveness to irrelevant stimuli. Cortical activation to these irrelevant stimuli was the primary measure of interest (auditory cortex to sound or motion-sensitive cortex [middle temporal area, MT] to motion). Groups were compared for activation levels across the task, and correlations were run between activation and clinical characteristics.
Results: Patients performed the task equivalently to healthy controls, and all participants had worse performance as the task became more difficult. Patients who had a more severe illness presentation at the time of scanning displayed auditory cortex activation to irrelevant sounds that was lower at all difficulty levels relative to controls, whereas clinically stable patients' auditory cortex activation was similar to that of healthy controls. Among patients reporting current, daily auditory hallucinations, the louder they reported the hallucination to be, the lower their auditory cortex activation was to irrelevant sounds. Reduced auditory cortex response was also associated with worse cognitive function. For irrelevant visual motion, a different pattern of results was found. Regardless of current symptom severity, patients displayed reduced activation in MT, and did not show relative reduction in activation to the irrelevant motion as the attention task become more difficult. Activation in MT among patients was not associated with symptom severity or cognitive function.
Conclusions: When sensory cortex response to irrelevant stimuli was noted in psychosis patients, it was reduced relative to controls and not modulated in correspondence with attention task difficulty. This could reflect a failure of top down control mechanisms, in that there was no modulation of response as the attention task increased in difficulty. Alternatively, it suggests active psychosis serves as an additional internal demand, reducing available resource for processing external, irrelevant stimuli. The association of abnormal auditory cortex response, but not visual cortex response, with greater symptom severity and poorer cognitive function fits with hypotheses of temporal lobe as a key structure for illness pathophysiology.
Keywords: psychosis, hallucination, attention, fMRI.
Disclosure: Nothing to Disclose.

W78. Withdrawn

W79. Brain Activity in Empathy and Approach-Motivation Domains for High-risk Parents is Increased by Intervention and Inversely Related to Parenting Stress

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Background: The mother-child relationship is central to early human development and provides the foundation that supports social-emotional functioning across the life course. Mothers with histories of trauma-exposure and mental illness are at risk for diminished parenting skills and or sensitivity that place children at risk for adverse psychosocial outcomes. Certain neurological functioning, known to support parenting, is also impaired with mentally illness. Brain functions critical to both parenting and impaired by mental illness include the domains of "social processes" and "positive valence signal processing", their respective constructs of "Perception and Understanding of Others" (i.e. empathy") and "Approach Motivation", and sub-constructs of "Understanding Mental states" and "Effort Valuation". These are plausible trans-diagnostic constructs to understand brain function important for parenting and impaired by mental illness. These brain function domains have not been investigated toward mechanistic understanding and optimization of parenting interventions aimed at increasing parental reflective function about baby and self, emotion regulation, and motivation to choose caring behaviors.
Methods: We assessed a group of 29 trauma-exposed mothers of 2-7 year old children - 14 before and after an attachment-based parenting intervention and 15 on a treatment-as usual wait-list. The intervention, mom power, is a 10-week evidence based, relationship focused intervention. Pre/post intervention measures include the parenting

stress index (PSI), which is known to be associated with maternal psychopathology and child socio-emotional/behavioral outcomes, the working model of the child interview (WMCI) to assess maternal mental representations of their children, and videotaped mother-child behaviors to assess maternal sensitivity. Participant mothers underwent two brain imaging tasks pre and post intervention using tailored stimuli to elicit responses to each mother's own child: (1) Who's Crying: listen to 30 second-blocks of baby-cries with instructions: "imagine this is your-baby crying" or "just listen to the baby-cry"; and (2) a child empathy task which asks to "join with" vs. "observe" own and other infant faces of different affect. Data from Phillips 3T scanner were analyzed with SPM 8 analysis software.

Results: We tracked significant increases in brain activity as a function of parenting treatment ($n = 14$) and controlling for time and sham treatment-as-usual ($n = 15$), in response to own baby-stimuli in positive valence and social process domains ($P < 0.001$). Brain regions with increased response to "your-baby-cry" vs. "just-listen" include amygdala, precuneus, dorsal anterior cingulate cortex and dorsolateral prefrontal cortex (DLPFC). Brain activity was also increased for the "join" vs. "observe" own vs. other child picture, in the DLPFC and insula. Furthermore, brain activity in brain domains represented above was significantly inversely related to parenting stress ($P < 0.001$): for the own baby-cry task, in theory of mind regions of the precuneus, medial prefrontal cortex and temporoparietal junction, and for the own-child empathy task, in approach motivation regions of the amygdala and ventral striatum. Thus many of the same brain areas with increased response to baby stimuli as a result of parenting intervention were inversely active according to parenting stress.

Conclusions: Evidence-based and relationship-focused parenting interventions for mothers of young children, such as mom power, increase brain activity in brain circuits important for understanding others, approach motivation, emotion response and regulation during tasks requiring responses to their own child. We thus outline objective basic neural mechanisms of change through which parent-therapy acts on the maternal brain and may relate to stress reduction. These mechanisms may be used to evaluate brain systems for attachment, optimize interventions for parent-child relational problems, and suggest personally tailored brain imaging paradigms to explore trans-diagnostic domains of brain functioning.

Keywords: brain, baby-cry, empathy, motivation.
Disclosure: Nothing to Disclose.

W80. Brain Stimulation Induced Connectivity Between Amygdala and Ventral Cingulate in Humans

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Background: A critical interaction between amygdala and ventral anterior cingulate cortex (homologue) for regulating the amygdala and fear responses has been well established in non-human animals. Similarly, neuroimaging studies in humans have implicated abnormalities in this circuit across affective disorders. Given evidence of a causal role established in animals for the vACC in regulating the amygdala and fear behavior, this site is a critical target for neuropsychiatric interventions in humans. Transcranial magnetic stimulation is useful both as a probe of brain circuit integrity as well as a tool for brain stimulation treatment. However, it is unclear whether TMS to accessible surface regions of the brain can reliably influence deep brain areas such as the amygdala and vACC or, most critically, their interaction with one another.

Methods: Single pulse probe TMS was interleaved with whole brain volume fMRI recordings in 24 healthy right-handed individuals. TMS was delivered at a rate of 0.4 Hz at 120% motor threshold to the anterior medial frontal gyrus (aMFG) and posterior medial frontal gyrus (pMFG) on each side of the brain. Sites were chosen from ICA maps generated from resting fMRI data in a separate cohort thought to represent the salience and central executive networks, respectively. ANOVAs included network (aMFG/pMFG), stimulation hemisphere (left/right), and seed region (basolateral/centromedial amygdala) with dependent variables as connectivity z-scores between the amygdala and vACC (psychophysiological interaction for stimulation events relative to baseline).

Results: In response to induced connectivity (single pulse TMS) between the amygdala and ventral ACC measured with concurrent fMRI, there was a hemisphere effect (right > left) that was largely consistent across amygdala subregions (basolateral/centromedial) and stimulation site (anterior/posterior middle frontal gyrus). In terms of activation, pMFG stimulation was more successful in activating the vACC and amygdala compared with aMFG stimulation.

Conclusions: These results suggest 1) using non-invasive TMS brain stimulation to surface accessible prefrontal sites, it is possible to activate deeper brain regions implicated in anxiety, depression, and regulation of affect and 2) TMS to the right hemisphere can induce increases in amygdala-vACC connectivity, a circuit implicated in amygdala regulation and pathology among affective disorders. The results also suggest a benchmark for defining abnormalities in patients as well as a pathway through which neuromodulation may increase patients' abilities to regulate affect.

Keywords: transcranial magnetic stimulation, fMRI, affective disorders, cognitive neuroscience.
Disclosure: Nothing to Disclose.

W81. Exclusion Hurts: Differential Neural Response to Exclusion than Inclusion by Childhood Friends and Strangers

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Background: Peer relationships and friendships play a major role in the cognitive, emotional and social development in childhood (Hartup, 1996). Peer relations in

childhood are characterized by co-operation, competition and conflict. Social rejection and acceptance are common in childhood and can be studied in the laboratory by a virtual game called Cyberball (William & Jarvis, 2006). Previously, we used Cyberball to probe real time brain activity with ERP's (Crowley et al., 2009; Crowley et al., 2010). Subsequently, in research conducted on high salience kin relationships, we identified P2 and slow wave differences on exclusion by kin in mother-child dyads (Sreekrishnan et al., 2014). Here in, we examine the differences in neural response (P2 and slow wave) of exclusion and inclusion events in a Cyberball paradigm using best friend dyads, the one other highly salient relationship in childhood. Further, we examined the role of friendship quality and psychological distress on the exclusion and inclusion event related ERP's.

Methods: Forty-six children (twenty-three best friend pairs: Female Age = 10.86, SD = 1.32; Males Age = 10.66, SD = 1.28) were recruited via mass mailings along with their best friends. Children filled out Children's Depression Inventory, Multidimensional Anxiety Scale for Children and Friendship Quality Questionnaire before playing the Cyberball game. A composite psychological distress score was calculated from the anxiety and depression scores. Cyberball game consisted of the participant playing with two pre-programmed players (participants were led to believe that the other players were real and one was a friend other a stranger) that throw and receive a virtual ball. The game consists of inclusion events where the participant received a ball from the friend or the stranger and exclusion events where the participant is excluded and does not receive the ball from the friend or the stranger. Standard protocol was used to obtain a high density EEG with a 128 Ag/AgCl electrodes. Post collection processing was conducted per standard procedures and Ocular Artifact Detection was conducted to remove eye movements and blinks. We utilized the left frontal are EEG net channels 12, 18, 19, 20, 22, 23, 24 for the ERP analysis. Data was collected and analyzed in best friend dyads. Initially, we evaluated the inclusion based ERP's (P2 100-300 msec and Slow wave 450 – 900 msec) of friend and stranger and exclusion based ERPs (P2 and slow wave) of friend and stranger to identify activation patterns. Subsequently, a linear mixed model ANOVA with repeated measures was used to test the effects of identity (friend vs stranger), friendship quality and psychological distress on the inclusion and exclusion based ERPs.

Results: In the inclusion trials, identity (friend vs stranger) or the interaction of identity and friendship quality was not significantly associated with P2 ($F < 0.717$, $p > 0.402$) or Slow wave ($F < 2.276$, $p > 0.140$). Similarly, neither identity nor the interaction of identity and psychological distress was significantly associated with P2 ($F < 0.791$, $p > 0.379$) or slow wave ($F < 3.646$, $p > 0.064$). In the exclusion trials, similar to the inclusion trials, identity or the interaction of identity and friendship quality was not significantly associated with P2 ($F < 0.099$, $p > 0.755$) or slow wave ($F < 0.265$, $p > 0.610$). However, identity (F1, 38 = 5.70, p = .022) and the identity x psychological distress interaction (F1, 38 = 15.44, p = .000) were significantly associated with P2. The correlations of P2 with exclusion by friend was r = -0.366, p = 0.020 and exclusion by stranger was r = 0.481, p = 0.002. In the slow wave analysis, similar to the P2 analysis, identity (F1, 38 = 6.76, p = .013) and the identity x psychological distress interaction (F1, 38 = 10.795, p = .002) were significantly associated with slow wave. The correlations of slow wave with exclusion by friend was r = -0.431, p = 0.006 and exclusion by stranger was r = 0.354, p = 0.025.

Conclusions: The results obtained in this study were intriguing and suggest no neural activation differences in inclusion analyses suggesting acceptance by a friend or a stranger in this virtual paradigm are equally activating. Friendship quality was not associated with neural response in both the inclusion and exclusion trials. However, the activation patterns in the inclusion and exclusion trials differed in the context of psychological distress. Although psychological distress was not associated with neural activation in the inclusion trials, in highly distressed subjects, exclusion by a stranger was associated with increased activation of P2 and slow wave suggesting higher utilization of attentional resources and evaluative processes after the exclusion event. The results highlight the differential role of psychological distress in acceptance versus rejection based friend and non-friend peer relationships. Further research should focus on neurocognitive pathways of rejection sensitivity associated with psychological distress and the role of internal self-regulation in peer relationships.

Keywords: Cyberball, ERP, inclusion and exclusion, psychological distress.

Disclosure: Nothing to Disclose.

W82. Daily Marijuana Use is Not Associated with Brain Morphometric Measures in Adolescents or Adults

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Background: Recent research has suggested that marijuana use is associated with volumetric and shape differences in subcortical structures including the nucleus accumbens and amygdala in a dose dependent fashion. Replication of such results in well-controlled studies is essential to clarify the effects of marijuana.

Methods: We examined brain morphology in a sample of adult daily marijuana users (n = 29) versus non-users (n = 29) and a sample of adolescent daily users (n = 50) versus non-users (n = 50). Groups were matched on a critical confounding variable, alcohol use, to a far greater degree than in previously published studies. We acquired high-resolution MRI scans and investigated group differences in gray matter using voxel-based morphometry, surface-based morphometry, and shape analysis in structures suggested to be associated with marijuana use: the nucleus accumbens, amygdala, hippocampus, and cerebellum.

Results: No statistically significant differences were found between daily users and non-users on volume or shape in the regions of interest: effect sizes suggest that the failure to find differences was not due to a lack of statistical

power, but rather was due to the lack of even a modest effect. The very modest effect sizes noted for the structures in the present study are consistent with the average effect size of marijuana on morphology across other published studies.

Conclusions: In sum, the results indicate that, when carefully controlling alcohol use, gender, and age, there is no association between marijuana use and standard volumetric or shape measurements of these subcortical structures.

Keywords: marijuana, morphology, adult, adolescent.

Disclosure: Nothing to Disclose.

W83. Bootstrapping the Hippocampus? Atypical Learning Characterizes Adolescents with Autism Spectrum Disorders

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Background: Individuals with autism spectrum disorders (ASD) display an uneven pattern of abilities and disabilities in learning and memory. The prevailing view is that they exhibit intact semantic memory for items, facts, details, and routines, but manifest impairments in episodic memory and in generalizing learning from one context to the next. The underlying neurobiology including the role of deficits in the medial temporal lobe (MTL) including the hippocampus (HC), and the prefrontal cortex (PFC) remains unclear. Based on results of a study of transitive inference, our group has argued that young adults with ASD use learning and memory strategies that are more reliant on the hippocampus than on the PFC, given their cognitive control deficits. Here we continue to investigate this contention in adolescents with ASD, using behavioral measurements designed to delve more deeply into MTL, HC, and PFC contributions to encoding, retrieval, strategy use, and the generalization of learning.

Methods: Participants included well-characterized 12-18 year olds with ASD ($n = 27$; mean age = 14.8 years) and age, gender, and IQ matched participants with typical development (TYP) ($n = 25$; mean age = 14.8 years). To assess MTL and HC contributions to learning and memory they were administered the Relational and Item-Specific Encoding task (RISE; Ragland et al., 2012). On the RISE, they were asked to make "living/non-living" (item-specific) judgments; determinations about whether one stimulus fits inside the other (relational) judgments; and to provide confidence estimations for their responses. Accuracy rates, and d' (hit rate - false alarm rate) served as measures of performance. Relative contributions of familiarity and recollection also were analyzed using receiver-operating characteristics (ROCs) analyses. To assess PFC contributions to learning and memory, participants completed the California Verbal Learning Test-Children's Version (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994). In CVLT-C participants were asked to learn a "shopping list" containing items from three semantic categories over a series of 5 trials. They were then tested at short and long delays and after the presentation of a different interfering list. The use of semantic and serial clustering strategies also was examined. ANOVAs and t tests were used to test for between-group differences. All statistical analyses were performed using SPSS 22.

Results: Contrary to the prevailing view that those with ASD exhibit intact item processing alongside impaired relational processing, the ASD group showed poorer item-specific accuracy ($t(49) = 2.2$, $p = .0.03$) and d' ($t(49) = 2.7$, $p = .009$), but comparable relational encoding accuracy and d' relative to TYP on the RISE . The ASD group also showed a relatively reduced contribution of familiarity when making relational judgments ($t(49) = 2.3$, $p = .025$). This pattern of findings may suggest that those with ASD benefitted disproportionately from the deeper spatially-oriented encoding involved in the relational condition because they possess a relatively intact HC and/or other posterior MTL regions (e.g. the parahippocampal cortex) that support recollection alongside impairments in processes supporting familiarity on the RISE. Findings from the CVLT-C also were somewhat unexpected. Relative to TYP, the ASD group showed poorer list learning ($t(52) = 2.2$, $p = .032$) and free and cued recall at both short [free recall: $t(52) = 3.345$, $p = .002$; and cued recall: $t(52) = 3.32$, $p = .002$] and long delays [free recall: $t(52) = 4.74$, $p < .001$; and cued recall: $t(52) = 3.23$, $p = .002$]. They also exhibited lower recall consistency ($t(52) = 3.82$, $p < .001$) with more perseverations ($t(52) = 2.17$, $p = .034$), suggesting they have prefrontally-mediated cognitive control deficits which impede the deep encoding of semantic materials that facilitates generalization (Shohamy & Wagner, 2008). However, both groups relied comparably on semantic and serial clustering strategies which are thought to require processing by the hippocampus.

Conclusions: Findings are inconsistent with the commonly held view that individuals with ASD exhibit intact lower-level learning and semantic memory and impaired higher level learning and episodic memory. Instead, they suggest that those with ASD may actually be relatively worse at lower-level learning of items that is prefrontally-mediated or that involves areas of the anterior temporal system (AT; Ranganath & Ritchey, 2012) including regions of the lateral and orbitofronal cortices, and the perirhinal cortex, and relatively better at relational versus item-specific encoding under the right conditions such as those involved in spatial processing which is sub-served by a relatively more intact posterior medial system (PM; Ranganath & Ritchey, 2012) including the hippocampus and parahippocampal cortex. Replication of these findings in behavioral and neuroimaging studies, would have significant implications for teaching children with ASD because it would clarify their relative strengths and challenges as supported by neurobiology. Interestingly, this pattern of findings also represents a double dissociation from that found in individuals with schizophrenia, who show deficits in relational encoding and recollection alongside intact item specific encoding and familiarity.

Keywords: learning and memory, recollection and familiarity, hippocampus, adolescents.

Disclosure: C.S. Carter has served as a one-time consultant for Pfizer, Merck, Lilly, Servier. M.Solomon and remaining co-authors have no disclosures.

W84. Nonlinear Dynamical Classification of the COGS-2 Mismatch Negativity Data in Schizophrenia Patients Using Delay Differential Analysis

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Background: There is compelling evidence that sensory processing impairments contribute to the cognitive and psychosocial dysfunction affecting the majority of schizophrenia (SZ) patients. Mismatch negativity (MMN) is a translational EEG (electroencephalography) measure with promising applications for use as both an endophenotype in genomic studies and as a biomarker in clinical outcome studies. Although MMN amplitude is already regarded as an informative probe of the neural substrates of sensory processing dysfunction in neuropsychiatric disorders, conventional approaches to EEG analysis do not access the full wealth of information contained in the whole EEG signals. Delay Differential Analysis (DDA) is a time-series data analysis tool derived from embedding theory in nonlinear dynamics that may improve our understanding of the nature of neurophysiological impairments in SZ. DDA reveals nonlinear as well as spectral properties of an underlying dynamical system and can serve as a time-domain analysis tool complementary to Fourier analysis and other higher order statistics. This powerful approach utilizes embeddings, a framework in nonlinear dynamics where mappings of time series can be used to obtain insights about the non-linear invariants of the system without requiring direct access to all variables. We hypothesized that DDA applied to MMN recordings would significantly differentiate SZ from nonpsychiatric comparison subjects (NCS).
Methods: Preliminary DDA analyses were applied to single trial EEG data obtained from 20 subjects (NCS $n = 10$, SZ $n = 10$) who underwent MMN testing as part of their participation in the Consortium on the Genetics of Schizophrenia (COGS-2) study.
Results: DDA significantly differentiated groups based on single trial analyses. The area under the ROC curve (receiver operating characteristic) was 0.74. We obtained this results by using repeated random subsampling cross-validation (CV). We plan to refine the analysis by applying three different CV frameworks to test for instationarities in the trials and for timing differences of the MMN.
Conclusions: DDA appears to be a promising computational approach for capitalizing on information contained in whole EEG signals in order better understand and perhaps predict response to therapeutic interventions in neuropsychiatric disorders. Future planned analyses will refine and apply these DDA methods to the full cohort of $n = 1600$ COGS-2 participants who underwent COGS-2 MMN testing.
Keywords: Schizophrenia, EEG, Biomarkers, Computational Neuroscience.
Disclosure: Nothing to Disclose.

W85. Pre-, Peri-, and Post-Deployment Trajectories of Health over Four Years of Follow-up in the Ohio Army National Guard Mental Health Initiative (OHARNG-MHI)

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Background: The burden of post traumatic stress disorder (PTSD) and depression in the military is well documented and co-occurring alcohol misuse is common, but few studies have documented longitudinal trajectories of these disorders, and none have considered how co-occurring alcohol misuse modifies these trajectories. The primary aim of the OHARNG-MHI is to examine the role of pre-, peri-, and post-deployment experiences, both military and civilian, in jointly contributing to trajectories of psychopathology, psychological adjustment, and resilience. This particular analysis identifies vulnerable subgroups by studying trajectories of depression and PTSD symptoms after deployment across four waves.
Methods: Among 3457 subjects enrolled into Waves 1-4 from 2008-2012, a cohort of 1199 were identified as having completed at least two study waves, being deployed within two years of baseline, and having experienced a traumatic event. All subjects with depression, with or without PTSD ($n = 727$), completed the Patient Health Questionnaire-9 (PHQ-9); those who also had co-occurring PTSD completed the PTSD Checklist (PCL). Subjects with PTSD ($n = 472$) completed both the PHQ-9 and the PCL using the same traumatic event defined as their worst of all study waves. Time-stable risk factors at baseline (area of conflict to which the soldier was deployed in their most recent deployment, low education/income, childhood adversity, marital status, $10 +$ lifetime traumas, $4 +$ lifetime stressful events) and time-varying covariates (past-year alcohol misuse, past-year PTSD, past-year depression, and cumulative traumas and stressors) were used to identify membership into different latent trajectory groups and to assess the effect of alcohol misuse on observed trajectories. Using the PHQ-9, depression symptoms were modeled assuming a zero-inflated Poisson distribution in the 727 soldiers. PTSD symptoms were modeled assuming a censored normal distribution using the PTSD Check List symptom scale in 472 soldiers and were questioned about the same worst index event throughout all follow-up interviews. Alcohol misuse was defined as having either past-year abuse or dependence defined by the DSM-IV. SAS-callable proc traj was used to estimate output trajectories. PTSD diagnosis at each time point was used as a time-varying covariate to see if it significantly altered outcome, and conversely, depression at each time point was used as a covariate in the PTSD trajectories.
Results: Following combat trauma and after the follow-up period, 46% of soldiers were resistant to the development of PTSD symptoms, 38% experienced mild PTSD symptoms that remitted, 11% mild chronic PTSD symptoms, and 5% chronic moderately severe PTSD. Vulnerable subgroups were identifiable at baseline as low income, low education,

and high number of lifetime traumatic events. 55% of soldiers were resistant to the development of depressive symptoms, 20% experienced remitting mild depression symptoms, 13% displayed delayed onset of two symptoms of depression, and 12% showed chronic dysfunction. Trajectories of Depression: Baseline lifetime stressors predicted chronic dysfunction three-fold. The absence of childhood trauma, not being married/being single, not being deployed to a conflict area, and having few lifetime stressors were associated with resistance to the development of depressive symptoms. Whereas the addition of alcohol abuse or dependence had no effect on the 55% who were resistant to depression symptoms across all four waves, all other subgroups misusing alcohol experienced a worsening of depressive symptoms. Of the 727, the 13% who were resistant at month 7 and only worsened minimally over the 45 months were particularly vulnerable to the detrimental effects of alcohol misuse, which resulted in a 180% increase in depression symptoms across the four waves; the two remaining trajectory groups showed moderate increases in symptomology. Trajectories of PTSD: A high level of potentially traumatic events at baseline made soldiers nearly 12 times more likely to fall into the chronic dysfunction group. Being deployed to an area of conflict was associated with constant mild symptoms. Of the 472, 46% experienced no PTSD symptoms at month 7 and went on to be completely resistant to the development of PTSD symptoms at all four time points. 38% had mild subsyndromal symptoms that gradually remitted over 45 weeks, 11% who had persistent constant mild symptoms of PTSD continued to do so, and 5% who had severe chronic symptoms worsened over time. The impact of those misusing alcohol was compared to those not misusing alcohol. The addition of alcohol misuse mildly worsened subjects in all four groups, with the largest effect being a 9.
Conclusions: Most soldiers fell into the low-symptoms groups and were resistant to both PTSD and depression. The primary predictors of chronic dysfunction were low income, low education, and a high number of lifetime traumas and stressors. The potential influence of lifetime risk factors on trajectories suggests that a life course perspective (including pre-, peri-, postdeployment inquiry) is critical in the investigation of psychopathology in service members.
Keywords: Trajectories, Suicide, PTSD, Alcohol Use Disorders.
Disclosure: Nothing to Disclose.

W86. Prevalence of New-onset Psychosis in U.S. Service Members Deployed to Kandahar, Afghanistan: Implications for Training Psychiatric Technicians

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Background: Psychotic disorders usually present in late adolescence-early adulthood; often in response to physical and emotional stress. Many U.S. Military Service Members (SM) deployed in support of Operation Enduring Freedom are in this age range and are exposed to significant stressors including separation from friends and family, demanding schedules, and threat of physical danger. Military psychiatric technicians are first-line treatment providers for SM with mental health problems. In this performance improvement project, we sought to establish the prevalence of new-onset psychosis in a deployed setting in order to determine the level of training on psychotic disorders appropriate for military psychiatric technicians.
Methods: The population of interest was defined as the number of individuals presenting for mental health care/evaluation at the NATO Role III Hospital in Kandahar, Afghanistan, over the period 01 JAN 2012 – 31 DEC 2013. Cases of psychosis were determined by examination of the medical record in Armed Forces Health Longitudinal Technology Application-Theater version (AHLTA-Theater). Any symptoms of psychosis led to case inclusion even if the ultimate diagnosis was not of a psychotic disorder.
Results: Medical records from 2290 individuals were examined and 21 cases with psychotic symptoms were identified. Three were non-U.S. SM (one Albanian Army, one contractor, one DoD civilian employee). The prevalence rate of psychosis among all mental health evaluations was 0.9%. The average age of those with psychosis was 30 ± 9.5; (range 20-53). Diagnoses were 24% psychotic disorder (delusional, schizophrenia/schizophreniform), 43% psychosis NOS, 19% mood disorder (bipolar, major depression with psychotic features), and 14% other (including PTSD).
Conclusions: Given the prevalence rate of nearly 1%, and the number of SM seen by mental health annually at the Kandahar Role III, psychiatric technicians can expect to see about 7 new cases of psychosis during a typical 9-month deployment. Therefore, training on recognition and management of psychotic symptoms in an acute setting would be extremely useful for deployed psychiatric technicians.
Keywords: psychosis, military, prevalance.
Disclosure: Nothing to Disclose.

W87. High Familial Clustering of Tic Disorders and OCD in a Population-based Cohort

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Background: Tic disorders, including Tourette syndrome (TS) and chronic tic disorder (CT), and obsessive-compulsive disorder (OCD) are notable for phenotypic overlap and co-occurrence in individuals and families. The causes of TS/CT and OCD remain largely unknown. Studies of familial and environmental risk factors for these disorders have largely relied on small or non-population based samples, rendering them vulnerable to ascertainment bias and lower precision. An approach available in recent years to circumvent these issues is to use national health registries, which provide a wealth of data for epidemiologic and etiological analyses. The Danish registry system is one such novel resource for prospectively examining risk factors for TS/CT and OCD with minimal ascertainment bias. We

utilized these registries to examine the sibling and parent-offspring recurrence risk and cross-disorder risk for TS/CT and OCD. We also assessed the role of parental age, a known risk factor for neuropsychiatric conditions such as autism and schizophrenia, in TS/CT and OCD.
Methods: We accessed relevant Danish registries to identify all individuals with TS/CT (ICD-8 code 306.2 and ICD-10 codes 95.1 and 95.2) and OCD (ICD-8 code 300.3 and ICD-10 codes F42.0, F42.1, and F42.2). Recurrence risk (RR) was defined as the likelihood that an individual with an oldest sibling (or parent) with TS/CT or OCD was affected by the same disorder, compared to an individual without an affected oldest sibling (or parent). Prevalence and RR were estimated using Kaplan-Meier methods and relative RRs were calculated using Cox regression. Parental age was divided into three age groups: <35, 35-39, and $40+$ years. The relative risk for TS/CT or OCD associated with parental age was estimated using Cox regression. We also defined a sibling subcohort (including families with at least one individual diagnosed with TS/CT or OCD), calculating relative risk using stratified Cox regression, to adjust for genetic and environmental factors shared among siblings.
Results: Of 1,741,271 individuals born from 1980-2007, 5,596 had a TS/CT diagnosis and 6,191 had an OCD diagnosis. Prevalence was 0.42% (95% CI, 0.41-0.43%) for TS/CT and 0.84% (95% CI, 0.81-0.87%) for OCD. The TS/CT sibling RR was 9.88% (95% CI, 8.02-12.16%); for OCD the sibling RR was 4.01% (95% CI, 2.78-5.76%). Individuals with an oldest sibling with TS/CT were 18 times more likely to be diagnosed with TS/CT (adjusted hazard ratio [aHR] 18.63; 95%CI, 15.34-22.63) when compared to individuals without an oldest sibling with TS/CT. Those with an oldest sibling with OCD were 5 times more likely to be diagnosed with OCD (aHR 4.89; 95%CI, 3.45-6.93). The parent-offspring RR for TS/CT was 19.00% (95%CI, 14.09-25.34%) and for OCD was 4.06% (95% CI, 2.85-5.78%). Individuals whose parent had TS/CT were 61 times more likely to have a TS/CT diagnosis (aHR 61.02; 95% CI, 44.43-83.82) while those whose parent had OCD were 6 times more likely to have an OCD diagnosis (aHR 6.25; 95% CI, 4.82-8.11). Cross-disorder risk was also significant. TS/CT in the oldest sibling was associated with an aHR of 3.98 for OCD (95%CI, 2.58-6.12); OCD in the oldest sibling was associated with an aHR of 4.88 for TS/CT (95%CI, 3.15-7.56). Cross-disorder analyses were similar when excluding oldest siblings with a dual diagnosis of TS/CT and OCD. Individuals whose parent had TS/CT were 10 times more likely to have an OCD diagnosis (aHR 10.27; 95% CI, 5.17-20.39); those whose parent had OCD were 3 times more likely to have a TS/CT diagnosis (aHR 3.20; 95% CI, 2.22-4.62). Increasing paternal age was associated with a small increased risk for OCD when mothers were under age 35 (paternal age 35-39 aHR 1.13, 95% CI 1.04-1.23; paternal age $40+$ aHR 1.11, 95%CI 0.96-1.28). In the sibling subcohort, increasing paternal age was associated with a small increased risk for OCD with maternal age 35-39 or $40+$, while increasing maternal age was associated with a small decreased risk for OCD with paternal age under 35; increasing paternal age was associated with a small decreased risk for TS/CT with maternal age under 35. Otherwise, the risk of TS/CT or OCD in both the population and sibling cohorts was independent of paternal and maternal age.
Conclusions: Based on a large, population-based national sample, our results indicate that TS/CT and OCD have high recurrence risk in siblings and in offspring of affected parents. The RR for TS/CT is profound and substantially higher than the RR for OCD. The cross-disorder risk for TS/CT and OCD is also significant. The $\sim$10% sibling RR for TS/CT and $\sim$4% sibling RR for OCD, combined with the $\sim$19% parent-offspring RR for TS/CT and $\sim$4% parent-offspring RR for OCD, provide an important clinical framework for identifying individuals at risk. Our results suggest that overall parental age is not reliably associated with TS/CT or OCD. The strong familial clustering of TS/CT and OCD reflects an important role for genetic and/or shared environmental factors. In future studies we will investigate the role of specific environmental risk factors utilizing Danish registry data. This work will synergize with large-scale genetic analyses that will be performed in this population to produce unprecedented insights about the etiology of TS/CT and OCD.
Keywords: Tic disorders, Obsessive-compulsive disorder, Recurrence risk, Parental age.
Disclosure: Nothing to Disclose.

W88. Prenatal Nicotine Exposure and Risk of Schizophrenia in a National Birth Cohort

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Background: We sought to investigate the relationship between prenatal nicotine exposure and risk of schizophrenia. Cigarette smoking during pregnancy is one of the most common toxic exposures during fetal life: approximately 20-25% of women smoke during pregnancy. Nicotine and cotinine, its main metabolite, readily cross the placenta into the fetal bloodstream. Prenatal exposure to this toxin alters transmission of acetylcholine, dopamine and other neurotransmitters, causes impaired cerebral inhibition, alters neuronal proliferation and survival, and is associated with cortical thinning. In this study, we assayed maternal serum specimens for cotinine levels in schizophrenia cases and controls from a large national birth cohort.
Methods: The study is based on the Finnish Prenatal Study of Schizophrenia (FiPS-S), which consists of virtually all pregnancies (over 1.5 million) in the country since 1983 with archived maternal prenatal serum specimens prospectively drawn during the first and early second trimesters. Cases were identified from a national psychiatric registry. Maternal cotinine levels during pregnancy were quantified in 977 cases of schizophrenia or schizoaffective disorder and controls matched 1:1 on birthdate, sex, and residence in Finland at time of case diagnosis.
Results: There were statistically significant associations between maternal cotinine and risk of schizophrenia. For every unit increase in log transformed maternal cotinine, the risk of schizophrenia was increased by 6% (OR = 1.06, 95% CI = 1.02-1.11, p = .008), adjusting for maternal age, province of birth, and any parental psychiatric disorder. The prevalences of high levels of maternal cotinine (defined

as > 50 ng/ml) were significantly greater in cases (20.2%) than controls (14.7%) (OR = 1.38, 95% CI = 1.05-1.82, p = 0.02), adjusting for these same covariates.
Conclusions: These findings provide the first biomarker-based evidence to date that maternal smoking is related to risk of adult schizophrenia. Although replication is required, and care is necessary to attribute the association as indicative of a causal relationship, these findings suggest that prevention of smoking in schizophrenia may lead to a reduction in risk of the disorder. The finding may also provide new insights into the pathogenic mechanisms that underlie schizophrenia.
Keywords: smoking, nicotine, schizophrenia, epidemiology.
Disclosure: Nothing to Disclose.

W89. Meta-analysis of Cytokine Alterations in Acutely Ill Psychiatric Patients: Comparisons Between Schizophrenia, Bipolar Disorder, and Depression

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Background: Schizophrenia, bipolar disorder, and major depressive disorder (MDD) have all been associated with immune system dysfunction, including aberrant blood cytokine levels. However, the pattern of cytokine alterations across disorders has not been compared. We performed a meta-analysis comparing and contrasting blood cytokine levels in acutely ill patients with schizophrenia, bipolar disorder and MDD, as well as the effects of treatment of the acute episode on cytokine levels.
Methods: We identified articles by searching Pub Med, PsychInfo, and ISI, and the reference lists of identified studies.
Results: 75 studies met the inclusion criteria, including 11 studies of bipolar disorder, 21 studies of major depressive disorder, and 43 studies of schizophrenia. Levels of four cytokines/receptors – IL-6, TNF-α, sIL-2R, and IL-1RA – were all significantly increased in patients with schizophrenia (first-episode psychosis and acutely ill patients with chronic schizophrenia), bipolar mania, and MDD compared to controls ($p < 0.01$ for each). There were no significant alterations in IL-2 levels in any of the disorders. Levels of IL-4 were significantly decreased and levels of IL-12 significantly increased in both MDD and schizophrenia ($p \leq 0.02$ for each). Following treatment for MDD, there was significant reversal of alterations in levels of IL-1β, IL-4, IL-6, IL-10, and IL-12. Levels of sIL-2R in schizophrenia significantly increased and levels of IL-1β and IL-4 significantly decreased following treatment for acute psychosis, and levels IL-1RA in bipolar disorder significantly decreased following treatment for acute mania.
Conclusions: Overall, there were many similarities in the pattern of cytokine alterations in schizophrenia, bipolar disorder, and MDD during acute illness episodes, raising the possibility of common underlying pathways for immune dysfunction in these disorders. Effects of treatment on cytokine levels were more robust for MDD than for acute mania or psychosis. These findings have important implications for our understanding of the pathophysiology and treatment of major psychiatric disorders.
Keywords: cytokine, meta-analysis, schizophrenia, mood disorders.
Disclosure: Nothing to Disclose.

W90. The Origin of Social Impairments in Schizophrenia; Developmental Trajectories and Potential Familial Influences

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Background: Impaired social functioning is one of the most disabling features of schizophrenia, and there is evidence suggesting that social alterations are already apparent prior to illness-onset. However, little is known about their origin and about whether premorbid social impairments represent familial vulnerability to- or markers of the illness. Traditionally, (mostly retrospective) studies examining premorbid social impairment in schizophrenia utilize very broad definitions, lumping together various social constructs into one social functioning score. Our objective was to separately investigate the origin of three key social impairments in schizophrenia – Social Engagement, Individual Autonomy and Functioning in Structured Environments.
Methods: Social behavioral data of almost half a million Israeli male adolescents assessed for the Israeli draft board were linked with data from the National Psychiatric Hospitalization Case Registry. Individuals later hospitalized with schizophrenia were compared to their unaffected sibling and with healthy sibling pairs. By means of univariate analyses of covariance, trend analyses, relative risk (RR) and group familial correlations, we examined the premorbid severity, developmental trajectory and familiality of impairments in Social Engagement, Individual Autonomy and Functioning in Structured Environments.
Results: The social dimensions Social Engagement and Functioning in Structured Environments, but not Individual Autonomy, were found to be familial and significantly related to higher risks of hospitalization for schizophrenia [Social Engagement (effect size = .47, $p < .0001$); Functioning in Structured Environments (effect size = .19; $p < .0001$); Individual Autonomy (effect size = .035; $p = .852$)]. Developmental trajectories differed for all three social dimensions. Whereas mild impairments in Social Engagement and Functioning in Structured Environments were already recognizable up to 15 years prior to hospitalization, Individual Autonomy seemed relatively preserved until the few years prior to first admission. In addition, while Social Engagement showed a steep further decline in the prodromal phase, trend analysis revealed no significant further decline prior to hospitalization in the ability to function well in structured environments.
Conclusions: Our results underscore both the significance and complexity of premorbid social impairments in schizophrenia. Although generally considered together, social impairments should not be considered as a single construct. Different impairments follow different developmental trajectories, of which at least two are present early on and are familial to some extent. Our findings provide clues about when to intervene and might suggest that a social construct like individual autonomy, which is less familial, is most receptive to treatment intervention.
Keywords: social impairments, schizophrenia, familiality, developmental trajectories.
Disclosure: Nothing to Disclose.

W91. Coexisting Psychiatric Illness in Depressed HIV-infected Individuals: Baseline Findings from a Real World Clinical Trial

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Background: While data addressing depression's impact on HIV outcomes grows, the effect of psychiatric comorbidity on HIV management remains poorly understood. We report on the prevalence of psychiatric comorbidity and its association with illness severity in depressed HIV patients.
Methods: As part of SLAM DUNC, a multi-site randomized controlled trial of depression treatment for HIV patients, 304 participants meeting criteria for current Major Depressive Disorder (MDD) were also assessed for other mood, anxiety and substance use disorders with the Mini-International Neuropsychiatric Interview, a structured psychiatric diagnostic interview. We also assessed baseline adherence, risk, and health measures.
Results: Complicated depressive illness was common. Only 17% of participants experienced MDD with no comorbid psychiatric diagnoses; 49% had comorbid dysthymia, 62% had ≥ 1 comorbid anxiety disorder, and 28% had a comorbid substance use disorder. Self-reported antiretroviral adherence did not differ by the presence of psychiatric comorbidity. However, psychiatric comorbidity was associated with worse physical health and functioning: compared to those with MDD alone, individuals with one or more comorbidities reported more HIV symptoms (4.8 vs. 4.1, p-value $= 0.01$), and worse mental health-related quality of life on the SF-12 (20 vs. 35, $p < 0.01$). The study's cross-sectional nature precludes assessment of causal relationships, and generalizability is limited to those with MDD.
Conclusions: For HIV patients with MDD, chronic depression and psychiatric comorbidity are the rule, and this complexity is associated with greater HIV disease severity and worse quality of life. Appreciating this comorbidity can help clinicians better target those at risk of harder-to-treat HIV disease, and underscores the challenge of treating depression in this population.
Keywords: Depression, Psychiatric Comorbidity, HIV, Quality of Life.
Disclosure: Nothing to Disclose.

W92. Independence of Familial Transmission of Bipolar Disorder and Attention Deficit Hyperactivity Disorder in a Community Based Family Study of Affective Spectrum Disorders

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Background: There is substantial evidence regarding the high magnitude of comorbidity of ADHD and bipolar disorder in both clinical (Aubry et al, 2014) and population based samples of adults (Merikangas et al, 2008) and youth (Youngstrom et al, 2010). However, the specific explanations for this strong association are still unresolved. The goal of this study is to investigate patterns and mechanisms for ADHD-bipolar comorbidity using data on familial transmission in a nonclinical sample of probands with a broad range of mood and comorbid conditions.
Methods: The sample included a total of 465 probands recruited from a clinically enriched community screening and their 563 directly interviewed adult first-degree relatives. ADHD and bipolar disorder subtypes were classified through a best estimate diagnostic procedure that included direct semi-structured interview and/or structured family history information from multiple informants.
Results: There was a very strong association between both bipolar I disorder and bipolar II disorder with ADHD within probands and within relatives (OR (95% CL): 5.34 (1.86, 15.36)). There was specificity of the familial association of bipolar I disorder (OR (95% CL): 8.16 (2.52, 26.4)) and ADHD (OR (95% CL): 2.88(1.3, 6.35)). However, there was no significant cross-aggregation between either bipolar I (OR (95% CL): 1.46 (0.43, 4.99)) or bipolar II (OR (95% CL): 1.15 (0.44, 2.98)) disorder subtypes with ADHD, suggesting that the familial transmission of bipolar disorder and ADHD is independent.
Conclusions: These findings confirm those of earlier studies of the familial aggregation of bipolar disorder and ADHD in the first nonclinical sample, and the largest family study of bipolar disorder to date. The results suggest the independence of the diatheses underlying these disorders, despite the strong comorbid association within individuals. Potential mechanisms for their association including developmental precursors, neurocognitive functioning, sleep problems, and temperamental traits such as impulsivity and disinhibition will be systematically evaluated. Unique Findings: These are the first analyses that investigate patterns of comorbidity and co-aggregation of bipolar disorder spectrum and ADHD in this large non-clinical family study. The familial patterns of potential correlates of ADHD and bipolar disorder including trait measures, neurocognitive function and sleep patterns have not been previously evaluated.
Keywords: bipolar disorder, attention-deficit hyperactivity disorder, familial aggregation, community based family study.
Disclosure: Nothing to Disclose.

W93. Antipsychotic Usage Patterns in the United States from 2003-2011 Extracted from the Medical Expenditure Panel Survey (MEPS)

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Background: Antipsychotics have changed the treatment of many psychiatric disorders, including schizophrenia, bipolar disorder, and treatment-resistant depression. As with many classes of medications, they have found popularity in

off-label uses. However, using these medications for off-label purposes is often not supported by robust evidence. Both first and second-generation antipsychotics are associated with significant side effects, including extrapyramidal symptoms and stroke for first-generation antipsychotics and weight gain and metabolic disturbances for second-generation antipsychotics. Trials comparing first- to second-generation antipsychotics to treat schizophrenia report little differences in efficacy; however, second-generation antipsychotics are associated with increased costs. Antipsychotic prescribing habits have received increased attention after some reports suggested these drugs may be over-prescribed in certain populations. The purpose of this study was to examine usage patterns of antipsychotics using the Medical Expenditure Panel Survey (MEPS) database from 2003-2011.

Methods: Data from 2003-2011 for patients of any age was collected from the MEPS, a set of large-scale surveys of families and individuals, their medical providers, and employers across the United States released by the Agency for Healthcare Research and Quality (AHRQ). The data were extracted and assembled, then the prescription file was linked to the personal level file (PLF) by each patient's unique ID. Each prescription event is recorded by reporting pharmacies in the database and the data weighted using the MEPS algorithm. Summary and descriptive statistical methods were used to generate the results. Analysis was done using SAS software version 9.3 (SAS Institute, Cary, NC, USA) and R programming language version 2.15.2 (R Foundation).

Results: Between 2003 and 2011, antipsychotic users increased by an average of 3.3%/year ($p = 0.01$). Over this time period, users of second generation antipsychotics increased by 725,000 while users of first generation antipsychotics decreased by 567,000, a 61% decrease in first generation usage. The most commonly used second generation antipsychotics were quetiapine, risperidone and aripiprazole and increases in their usage largely drove the increased antipsychotic use over the study period. Aripiprazole users increased most rapidly between 2003-11 ($p = 0.04$) from $\sim$1.6 million to $\sim$9.7, a roughly 5-fold increase when examining all adults. In those 65 years or older, quetiapine use increased faster than any other antipsychotic ($p = 0.02$). Most antipsychotic users are aged 19-64, comprising 80% of users. First generation antipsychotics were prescribed to users 65 years or older at a higher proportion than the 19-64 age group (1.5 ± 0.26 greater relative proportion in the $\geq$65 age group 2003-11). On average, $60 \pm 3\%$ of antipsychotic users are female. Between 2003-11 female users increased by an average of 2.3% and male users by 4.3%. Up until 2010, the majority of first generation antipsychotic prescriptions were written for medical conditions (51-60% of all first generation antipsychotic prescriptions between 2003 and 2009). Quetiapine was the most common second generation antipsychotic prescribed for non-psychiatric indications, with an average of 30% of prescriptions written for medical conditions between 2003-2010. Interestingly, trends in antipsychotic prescriptions written for medical purposes do not follow the same increases and decreases over time as antipsychotic prescriptions for psychiatric purposes.

Conclusions: According to data collected through MEPS, the total number of antipsychotic users has increased from 2003 to 2011, but exhibits variation year to year in the antipsychotic of choice and the clinical indication. These changes in usage patterns likely reflect changes in the FDA-approved uses and age limits, study results, and preferences of clinicians. The fact that these trends are not evident in prescriptions written for medical purposes may reflect the need for increased education to non-psychiatric providers or the need for further research on the benefits and harms of antipsychotic off-label use.

Keywords: Antipsychotics, Prescriptions, Usage, MEPS.
Disclosure: Nothing to Disclose.

W94. Clinical Predictors of Obesity in Mood and Psychotic Disorders: A Cross-sectional Study

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Background: Obesity and metabolic syndrome are prevalent in individuals with psychotic disorders and are related to increased mortality from cardiovascular disease and shorter life expectancy. Although elevated body mass index (BMI) has been associated with psychotropic medications, evidence for metabolic abnormalities in psychotic disorders predates the modern use of drugs. The present study examines predictors of elevated BMI across diagnostic categories of schizophrenia, schizoaffective disorder and bipolar I disorder. We hypothesized that overweight and obesity would be associated with diagnosis, and indicators of illness severity including poor social functioning, lifetime hospitalizations, prior suicide attempt, and family history of psychotic disorders.

Methods: In a cross-sectional study, we examine demographic and clinical predictors of overweight and obesity in a well-characterized cross-diagnostic sample of 262 patients with schizophrenia ($n = 59$), schizoaffective disorder ($n = 81$), and bipolar I disorder ($n = 122$). Inpatients and outpatients were recruited for an ongoing genetic association study of mood and psychotic disorders from 2006 to 2013. The Structured Clinical Interview for DSM-IV-TR was used for diagnosis and symptom measurement. For measurement of elevated BMI, we combined overweight (BMI of 25.0 to 29.9) and obesity (BMI of 30.0 or higher).

Results: Across diagnostic categories, the prevalence of overweight was 29.4% (77/262) and obesity was 33.2% (87/262), including 10.7% (28/262) of patients with grade 2 obesity and 6.1% (16/262) with grade 3 obesity. In multivariate logistic regression analyses controlling for age, gender and race, overweight and obesity combined (BMI $\geq$25) was significantly associated with a diagnosis of schizoaffective disorder, lifetime major depressive episode, presence of prior suicide attempts, and more than 5 lifetime hospitalizations. Overweight and obesity were negatively associated with a diagnosis of schizophrenia. After controlling for age, gender and race, elevated BMI was not associated with indicators of lower social functioning. Atypical and typical antipsychotic and mood stabilizer use were also not associated with elevated BMI in our sample.

There was no difference in atypical antipsychotic use between the three diagnostic groups.
Conclusions: We found that overweight and obesity were prevalent across diagnostic categories. Notably, factors related to affective components of psychotic disorders were found to be significant predictors of elevated BMI after controlling for age, gender and race. A diagnosis of schizoaffective disorder and lifetime major depressive episode predicted overweight and obesity combined, whereas schizophrenia was negatively associated with elevated BMI. Patients with schizoaffective disorder may have an underlying greater risk for metabolic abnormalities. Overweight and obesity were also associated with potential indicators of illness severity, including hospitalizations and prior suicide attempt. Identifying predictors of elevated BMI in patients with mood and psychotic disorders treated with psychotropic medications may aid clinicians in prevention of medical co-morbidities and psychiatric complications, in addition to providing phenotypes to further study metabolic disturbances in this population. Studies are needed to elucidate the nature of the directional relationship between obesity and mood and psychotic disorders, independent of medication effects.
Keywords: Obesity, metabolic syndrome, schizophrenia, bipolar disorder.
Disclosure: Dost Ongur: Scientific Advisory Board for Lilly in 2013. Guy Chouinard: 1 Invited guest lecture by Otsuka Pharmaceutical in 2014.

W95. Early Life Stress Affects the Expression of Neuronal Maturation Genes in the Paralaminar Nucleus of the Primate Amygdala

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Background: Early life stress (ELS) is implicated in the development of difficulties with emotional regulation, and anxiety. One mechanism by which ELS may impart these changes is by disrupting the development of brain regions involved in emotional processing. The amygdala, a structure involved in emotional responses, undergoes protracted postnatal development, implying that ELS may affect its maturation. In the amygdala, multiple nuclei undergo differential rates of maturation. The paralaminar nucleus (PL), a prominent structure in humans and primates, has a relatively late development compared to other nuclear regions. Consistent with this, our lab and others have shown that even in adult animals, the PL harbors morphologically immature appearing neurons that contain doublecortin (DCX) and the polysialylated form of neural cell adhesion marker (PSA-NCAM), two proteins expressed in post-mitotic neuroblasts. Since these cells are largely confined to the PL, this region may have unique vulnerabilities to ELS. Therefore, we examined whether ELS alters the expression of neuronal maturation genes in the PL and therefore may influence amygdala structure and function.
Methods: We used microarray and gene set enrichment methods to examine gene expression changes in the PL of tissue collected from 3-month old macaques maternally separated at 1 week or 1 month of age, relative to maternally reared counterparts (Sabatini et al., 2007). To examine whether gene expression changes were unique to the PL, we also isolated and looked at expression changes of the amygdalohippocampal area (AHA), a region lacking immature-appearing neurons. Regions were isolated by laser capture microdissection. mRNA was analyzed using Affymetrix Gene 1.0 ST arrays. For our analysis, we created a customized gene set comprised of 128 genes involved in early stages of neuronal maturation, relying on previous immunocytochemical data from our laboratory, and primary literature. For this initial study, we chose to cast a wide net to include any gene that played a documented role in neuroblast maturation, regardless of its other functions. We then tested the hypothesis that the set would be differentially expressed in the following two comparisons: 1) monkeys separated at 1 week vs. maternally reared monkeys and 2) monkeys separated at 1 month vs. maternally reared monkeys. We compared the gene set's average ALR to the average ALR for all genes on the chip using an unpaired 2-tailed Student's t-test with a p value threshold set at $p < 0.05$. As a second level of analysis, we then identified individual genes within the customized gene set that showed differential expression. To determine whether changes were PL-specific, we also ran both analysis levels with the AHA. Confirmation of differential gene expression was confirmed by qPCR and in-situ hybridization.
Results: Our results showed that our customized gene set was downregulated in the PL of monkeys separated at 1 week and at 1 month compared to maternally reared controls. In the AHA, the gene set was also downregulated in monkeys separated at 1 week, but upregulated in monkeys separated at 1 month. A comparison of the most affected genes for each comparison indicated that the gene signatures between the PL and the AHA were distinct. Of the neuronal maturation genes influenced by ELS, t-brain1 (tbr-1), a transcription factor that regulates glutamatergic neuronal maturation in the developing cortex and neurogenic zones, was specifically downregulated in the PL.
Conclusions: 1. Maternal separation alters the expression of genes involved in early stages of neuronal maturation in the PL and AHA. However, the gene signatures between the two regions are distinct, suggesting that ELS differentially affects its cellular constituents. This finding emphasizes the need to consider individual nuclei when examining the effects of stress on amygdala development. 2. tbr1 was uniquely downregulated in the PL of separated monkeys. Downregulation of tbr1 suggests that cells in the PL are affected by ELS in young monkeys, possibly by altering glutamatergic maturation programs.
Keywords: paralaminar nucleus, amygdala, early life stress, neuronal maturation.
Disclosure: Nothing to Disclose.

W96. Genome-wide Mapping of Methamphetamine Sensitivity in Commercially Available Outbred Mice

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Background: Sensitivity to the locomotor activating effects of methamphetamine (MA) shares overlapping neurocir-

cuitry with brain areas that are associated with reward. This sensitivity may contribute to risk for drug abuse disorders. Individual differences in initial sensitivity to MA are controlled in part by genetic factors; however, identifying genes underlying these differences has proven difficult. Mice, in principle, offer a powerful tool for elucidating the genetic basis of behavioral and physiological traits relevant to substance use disorders; yet conventional experimental crosses derived from inbred strains have only been able to identify large chromosomal regions rather than specific genes.

Methods: We have taken advantage of an extant outbred population that has been maintained using an outbred breeding scheme for more than 100 generations to identify and map narrow quantitative trait loci (QTL) associated with sensitivity to the locomotor stimulant response to MA. Male CFW mice ($n = \sim 1100$) were injected with saline (days 1 and 2) and MA (day 3; 1.5 mg/kg i.p.) and distance traveled was measured for 30 minutes. We used a novel DNA sequencing technique known as genotyping by sequencing (GBS) to obtain genotypes at ~ 100k markers across the genome. Next, GWAS was performed using a linear mixed model to account for confounding due to relatedness. Finally, we performed RNASeq on three brain regions (prefrontal cortex, hippocampus, and striatum) from a subset of animals in order to explore the network of correlations that exist between DNA sequence, gene expression values and methamphetamine sensitivity.

Results: We identified two narrow QTL peaks that reached genome-wide significance, on chromosomes 6 ($p = 9.03 \times$ 10-7), and 9 ($p = 1.58 \times 10$-6) that were associated with methamphetamine sensitivity. As compared to typical human disease GWAS results, the peak SNPs in each QTL region explained a large proportion of the genetic variation in MA sensitivity (rs223979909 located at 75.72 Mb on Chr 6 PVE = 2.6%; rs46497021 located at 117.76 Mb on Chr 9 PVE = 2.1%). In the QTL on chromosome 6, the peak SNP is located in a gene desert, however, the nearest gene to it is Ctnna2, which is a regulator of synaptic plasticity. It has been implicated in excitement seeking, ADHD, and substance use disorders (SUDs) in human GWAS, and therefore is a compelling candidate. The chromosome 9 QTL contained three genes within its region (Rbms3, Cmc1, Azi2). Although these genes have not been associated with SUDs to date, expression QTLs have been identified for two of these genes (Rbms3 & Cmc1), making them promising candidates for follow-up studies.

Conclusions: By exploiting the increased recombination frequency in outbred mice, we mapped behavioral and gene expression QTLs with significantly 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 substance use disorders, elucidate causative biological mechanisms, or assist in the development of putative treatment strategies.

Keywords: GWAS, methamphetamine, quantitative trait locus, substance use disorder.

Disclosure: Nothing to Disclose.

W97. N-Acetyltransferase Shati/Nat8l in the Dorsal Striatum Regulates Sociability and Motivation via Control of the Serotonergic Neuronal System in Mice

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Background: Psychiatric disorders, including major depression, are attracting significant attentio. However, the current therapeutic drugs for psychiatric disorders used in the clinical stage still have some problems. For example, the antidepressants that are prescribed widely for major depression, which affects approximately 16% of population and its age of onset encompasses the entire lifespan, they require weeks to months to produce a therapeutic response and are only moderately effective, thereby leaving over one-third of depressed patients resistant to drug treatment. Shati was isolated from the brain of a psychosis animal model treated with methamphetamine. Recently, Shati was identified as N-acetyltransferase-8 like protein (Nat8l), and then Shati/Nat8l was demonstrated to be the N-acetylaspartate (NAA) biosynthetic enzyme in the brain. NAA, an amino acid that is present at high concentrations in the brain, is considered to be a neuron-specific metabolite. NAA is condensed with glutamate and converted into N-acetylaspartylglutamate (NAAG). NAAG is widely distributed in the mammalian brain and is a highly selective endogenous group II metabotropic glutamate receptor type 3 (mGluR3) agonist. Furthermore, a postmortem study showed that the levels of NAA are significantly lower in the brain of subjects with major depression. The general lack of the Shati/Nat8l gene in mice was related to impairments in social interaction and exploratory behavior. These results suggest that Shati/Nat8l has an important role in emotional and psychiatric disorders. In the present study, we produced transgenic mice that overexpressed Shati/Nat8l (Shati/Nat8l-Tg mice) and mice that overexpressed Shati/Nat8l in the dorsal striatum using adeno-associated virus (AAV) vectors (AAV-Shati/Nat8l mice). This study suggests that Shati/Nat8l-regulated group II mGluR signaling and serotonergic neuronal system are possible new targets for the development of psychiatric medications.

Methods: Animals; Male mice of C57BL/6J strain, 8-week-old, were used. All experiments followed the NIH Guidelines for the Care and Use of Laboratory Animals and were approved by the committee for Animal Experiments of the University of Toyama. Generation of transgenic mice; The transgene cassette including the CAG promoter, which is constantly activated, and followed by a his-Shati/Nat8l sequence, was obtained from the CAG promoter-his Shati/Nat8l expression plasmid. Production and microinjection of AAV vector; The AAV vector plasmids contained an expression cassette, which comprised a human cytomegalovirus, followed by cDNA encoding either Shati/Nat8l (NM_001001985) or EGFP. In situ hybridization; To generate riboprobes, the PCR-amplified mouse Shati/Nat8l cDNA sequences (1133–1557 bp) were cloned into the pGEM-T Easy plasmid vector. Locomotor activity test; To measure the locomotor activity in a novel environment, a

mouse was placed for 60min in a acrylic cage with a black frosted Plexiglas floor ($45 \times 45 \times 40$ cm). Three-chamber social interaction test; Each chamber measured $20 \times 40 \times 22$ cm and the dividing walls were made of clear Plexiglas, where small square openings ($5 \times 3 \times 3$ cm) allowed access to each chamber. Tail suspension test; Individual mice were suspended by their tail; thus, the body dangled in the air facing downward for 6 min. The duration of immobility was recorded manually every 1 min using a stopwatch. Forced swimming test; Individual mice were placed in a transparent polycarbonate cylindercontaining water at 22 C to a depth of 18 cm and they were forced to swim for 6 min. In vivo microdialysis; A dialysis probe was inserted through the guide cannula and perfused with Ringer's liquid at a flow rate of 0.5 μl/min using a syringe pump. The dialysate was collected for 6 min from the dorsal striatum fractions and injected into an HPLC system. Three samples were used to establish the baseline levels of extracellular serotonin. Statistical analysis; Statistical differences among the values for individual groups were determined by an analysis of variance, followed by the Student–Newman–Keuls post-hoc test when the F ratios were significant ($p < 0.05$) (Prism version 5).

Results: In the Shati/Nat-Tg mice, Shati/Nat8l mRNA expression level in the whole brain of a specific line of the transgenic mice was 1.34 ± 0.05 times of that in the wild-type mice. We performed various behavioral tests to assess the phenotype of Shati/Nat8l-Tg mice. There was no difference of locomotor activity in the total counts between wild-type and Shati/Nat8l-Tg mice during a 60-min observation period. We performed a three-chamber social interaction test to examine sociability. The time spent with the stranger mouse by wild-type mice was significantly longer compared with that with the novel object. In contrast, Shati/Nat8l-Tg mice exhibited no difference in time spent between a stranger mouse and a novel object. In contrast, there were no differences in the immobility time in the tail suspension and in the forced swimming tests. We performed the three-chamber social interaction test. In trial 2, the AAV-mock mice spent significantly longer with the stranger mouse. In contrast, the AAV-Shati/Nat8l mice exhibited no difference in the time spent with the stranger mouse and with the novel object. AAV-Shati/Nat8l mice exhibited significant increases in their immobility time in the tail suspension and the forced swimming tests compared with the AAV-mock mice. In trial 2 of the three-chamber social interaction test, treatment with LY341495, restored the short time spent with the stranger mouse in AAV-Shati/Nat8l mice. Furthermore, in both the tail suspension and forced swimming tests, the increased immobility time of AAV-Shati/Nat8l mice was blocked by the same treatment with LY341495. The AAV-Shati/Nat8l mice exhibited unsociable and depressive phenomena; thus, we tested whether the behavioral abnormalities of AAV-Shati/Nat8l mice were recovered by treatment with a SSRI, fluvoxamine. The acute administration of fluvoxamine in AAV-Shati/Nat8l mice improved their decreased sociability as well as their behavioral despair. We measured the extracellular serotonin levels in their dorsal striatum via in vivo microdialysis. The basal levels of serotonin in the dorsal striatum of AAV-Shati/Nat8l mice were significantly lower than those of the AAV-mock mice.

Conclusions: Shati/Nat8l-Tg and AAV-Shati/Nat8l mice exhibited social withdrawa. The behaviors in AAV-Shati/Nat8l mice were recovered successfully by SSRI fluvoxamine treatment. Furthermore, AAV-Shati/Nat8l mice exhibited decreased extracellular serotonin levels in the dorsal striatum. Shati/Nat8l synthesizes NAA from aspartate and acetyl-CoA as an N-acetyltransferase. Subsequently, the enzymatic condensation of NAA and glutamate synthesizes NAAG, which has an agonistic effect in mGluR3-mediated neurotransmission. T In major depressive disorder, the serotonergic neuronal system must be controlled, because the cerebrospinal fluid levels of 5-hydroxyindoleacetic acid, a metabolite of serotonin, are low, and these subjects have significantly higher serotonin transporter potentials compared with healthy subjects according to positron emission tomography of the brain. Shati/Nat8l in the dorsal striatum should regulate depression-like behavior by controlling the serotonergic neuronal system via mGluR3 neurotransmission. These results indicate that Shati/Nat8l plays an important role in the depressive emotion via serotonergic neuronal system.

Keywords: Shati/Nat8l, social withdrawal, behavioral despair, serotonergic system.

Disclosure: Nothing to Disclose.

W98. Integrative Genetic Analysis of Methamphetamine's Motivational Effects in Mice

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Background: The subjectively positive effects of drugs are thought to contribute to early stages of drug abuse. Both drug abuse and the initially positive response to drugs are variable in humans and are known to have a genetic component. Epidemiological studies have established that individuals who report having a positive experience with drugs are at increased risk to develop drug addiction. Accordingly, we and others have suggested that the subjectively positive response to drugs, or 'drug liking' represents an intermediate phenotype for drug abuse. Individual variability in drug liking can be measured in mice and humans using the conditioned place preference (CPP) paradigm. CPP is the tendency for animals to spend more time in an environment paired with a rewarding drug. We anticipate that many of the genes and pathways underlying drug preference in mice will be common to humans.

Methods: We are conducting a genome-wide association study (GWAS) of CPP for Meth in a LG/J x SM/J advanced intercross line (AIL) of mice. AILs are highly recombinant outbred populations that can be used to identify specific genes associated with the trait of interest. In addition to CPP, we are using the LG/J x SM/J AIL to study the genetics of prepulse inhibition, locomotor activity and multiple other complex traits. We are using a genotyping-by-sequencing (GBS) strategy to genotype over 1,000 individuals from AIL generations 50-56. For a subset of mice we will also measure gene expression in the striatum,

hippocampus and prefrontal cortex using RNA sequencing. Integrating genotype, phenotype and gene expression data is a powerful approach that will accelerate the process of gene identification and provide insight into the biological mechanisms influencing the development of drug abuse.
Results: We have demonstrated that individuals in generations 50-55 (n = 1023) of the LG/J x SM/J AIL display robust CPP for Meth. On average, the amount of time spent by each mouse in a Meth-paired environment is significantly higher than the amount of time spent in the saline-paired environment after conditioning (p = 7.85x10-59). In addition, locomotor activity in response to Meth differs between the sexes, with females exhibiting increased activity relative to males (p = 1.76x10-5). A preliminary analysis of generations 50-51 (n = 362) revealed a suggestive association between CPP and a locus on chromosome 2. We also identified a promising association between a region on chromosome 7 and locomotor activity in response to Meth. We are in the process of genotyping additional animals to replicate these putative associations.
Conclusions: We anticipate that these studies will identify small chromosomal intervals associated with CPP and with gene expression traits. When a behavioral trait and a gene expression trait are associated with the same locus, this provides evidence that the gene expression trait may be causally related to the behavioral trait. In future studies we anticipate manipulating the expression of implicated genes to determine whether these manipulations have the expected phenotypic consequences.
Keywords: conditioned place preference, mouse model, drug abuse, genome-wide association study.
Disclosure: Nothing to Disclose.

W99. Mechanisms of Adolescent Tobacco Addiction

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Background: Adolescence represents a vulnerable period of heightened susceptibility to tobacco initiation and addiction. The mechanisms mediating the addictive properties of tobacco during adolescence remain poorly understood. Nicotine, a primary constituent in tobacco smoke, binds to nicotinic acetylcholine receptors (nAChRs) in limbic brain regions (e.g. hippocampus, amygdala, prefrontal cortex) to influence the processing of human emotion. The objective of our current study is to examine the role of hippocampal alpha(α)2-containing nAChRs in mediating developmental nicotine-induced changes in emotional memory processing, which may contribute to the addictive properties of tobacco. In adolescent mice, deletion of the Chrna2 gene (which encodes the α2 nAChR subunit) causes an absence of nicotine facilitation and suppression of CA1 hippocampal long-term potentiation (LTP). The Chrna2 gene has restricted expression within mouse limbic brain regions, including the oriens lacunosum-moleculare (OLM) GABAergic interneurons known to facilitate LTP in the hippocampal CA1.
Methods: In the present study we will show molecular genetic, electrophysiology, learning and memory behavioral data to examine the role of α2-containing nAChRs subserving developmental nicotine-induced changes in emotional memory processing in adolescent mice. Data will be presented using two mutant mouse lines: null mutant (Chrna2-/-) and a hypersensitive mutant (Chrna2L9'S).
Results: Our results illustrate that developmental exposure to nicotine via α2-containing nAChRs gates facilitation of long-term potentiation in the hippocampal CA1, as well as changes in adolescent emotional memory processing. The results presented highlight both the necessity and sufficiency of the α2 nAChR subunit throughout development to modify emotional memory processing, with and without developmental nicotine exposure.
Conclusions: We speculate that CA1 hippocampal OLM neurons expressing α2-containing nAChRs are responsible for developmental nicotine-induced changes in emotional memory processing, which may contribute to the addictive properties of tobacco use during adolescence.
Keywords: Addiction, Adolescence, Memory, Nicotine.
Disclosure: Nothing to Disclose.

W100. Differential Effects of Dorsal or Ventral Hippocampal CREB Deletion on Nicotine Withdrawal Phenotypes

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Background: Addiction to nicotine and ability to quit smoking are influenced by genetic factors. Therefore, it is important to understand how genes and pharmacotherapeutics interact. One well-characterized protein responsible for regulating gene expression is the transcription factor cAMP response element binding protein (CREB). CREB is required for the rewarding aspects of nicotine as measured in a place-conditioning paradigm (Walters et al, 2005). Correlative evidence suggests that CREB may also be required for behaviors manifested during nicotine withdrawal as well. CREB protein levels, phosphorylated CREB (pCREB) and CREB-DNA binding are differentially modulated throughout the brain following nicotine withdrawal (Pandey et al, 2001; Brunzell et al, 2003; Turner et al, 2013a). Additionally, recent studies have indicated that hippocampal-specific alterations in CREB signaling and synaptic plasticity may underlie certain nicotine withdrawal phenotypes (Turner et al 2013a; Turner et al 2013b). Therefore, this study examined the behavioral and biochemical effects of selective hippocampal CREB deletion in either the dorsal or ventral hippocampus during 24h withdrawal from chronic nicotine.
Methods: CREBloxP animals were injected with either AAV-CRE or AAV-GFP into the dorsal or ventral hippocampus. Four weeks following viral injection, animals were trained in the novelty-induced hypophagia (NIH) test for 12 days. Following training, animals were then equally divided into Saline, Nicotine, or 24h WD treatment groups and implanted with the corresponding osmotic minipump (Alzet). After 2 weeks of in vivo drug treatment, the animals

were then tested in the NIH paradigm followed by testing in the fear conditioning test. Tissues were collected after behavioral testing and are being analyzed for alterations in CREB signaling as well as for alterations in CREB target gene expression.
Results: Our studies indicate that ventral specific deletion of hippocampal CREB impacted anxiety withdrawal behaviors, but had no effect on cognitive withdrawal behaviors. In contrast, dorsal specific deletion of hippocampal CREB resulted in learning and memory deficits in the fear conditioning paradigm, but were not modulated by in vivo nicotine treatment or withdrawal. Ongoing experiments are evaluating which specific CREB targets are differentially bound and modulated in dorsal and ventral hippocampus during nicotine treatment and withdrawal, and thus may be responsible for mediating these effects.
Conclusions: Together, these data provide persuasive evidence for distinct roles of dorsal/ventral hippocampal CREB expression in mediating select nicotine withdrawal phenotypes. Future studies are directed towards understanding how this differential CREB activity in either the dorsal or ventral hippocampus can impact pharmacotherapeutic response during nicotine withdrawal. This line of investigation will advance both our understanding and implementation of personalized medicine for nicotine dependence.
Keywords: Nicotine, Withdrawal, CREB, Hippocampus.
Disclosure: Nothing to Disclose.

W101. Quantitative Trait Locus Mapping of Binge-Like Eating and its Motivational Components in a Reduced Complexity Cross: Implications for Genome-Wide Studies of Food "Addiction" and Eating Disorder Traits

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Background: Eating disorders, including Binge Eating Disorder, are highly lethal psychiatric conditions that exhibit a lifetime prevalence of 1 to 3%. Although they are heritable, genome-wide association studies in humans have yet to identify the causal genetic factors. Mammalian model organisms offer a powerful approach to studying the genetic basis of heritable traits that define eating disorders, including binge eating and its motivational components. Here, we wished to develop a forward genetic mouse model of binge-like eating with the goal of discovering novel genetic factors that contribute to this clinically important trait. We used C57BL/6 (B6) inbred substrains which have proven to be extremely useful in identifying novel quantitative trait genes for complex traits such as locomotor sensitization to cocaine (Kumar et al., Science, 2013, 342: 1508-12). C57BL/6J (B6J) and C57BL/6NJ (B6NJ) show robust strain differences in several behavioral traits, yet they contain only approximately 10,000 genetic variants. Thus, B6 substrains contain a markedly reduced genetic complexity compared to other laboratory inbred strains that typically possess millions of SNPs. Notably, in addition to cocaine behavioral traits, B6 substrains demonstrate differences in anxiety-like behavior – because both substance abuse and anxiety are co-morbid with binge eating, a cross between B6 substrains permits the ability to determine whether there is a shared genetic basis.
Methods: We used a conditioned place preference (CPP) procedure that allowed us to measure both consumption and conditioned reward for palatable food (PF). Outbred CFW mice, B6J mice, B6NJ mice, B6J x B6NJ-F1 mice, and -F2 mice ($N = 125$) were assessed for initial preference for the palatable food-paired side in a two-chamber design on Day 1. On Training Days 2, 4, 9, 11, 16, 18, and 23, mice were provided limited access to a porcelain dish containing palatable food pellets (5-TUL, Test Diet®, St. Louis, MO) for 30 min. On Training Days 3, 5, 10, 12, 17, and 19, mice were provided a clean, empty porcelain dish with no food for 30 min. Mice were assessed weekly for conditioned place preference for the palatable food-paired side (PF-CPP) on Days 8, 15, and 22. On Day 23, mice were assessed once again for binge-like eating. B6J, B6NJ, and F2 mice were also assessed for anxiety-like behavior in the elevated plus maze (EPM). All behavioral data were video recorded and tracked using AnyMaze software (Stoelting Co., Wood Dale, IL). Quantitative trait locus (QTL) mapping was conducted for palatable food consumption, PF-CPP, and EPM behavior in R/qtl using 96 informative markers (1000 permutations; $p < 0.05$).
Results: Outbred CFW mice exhibited a nine-fold escalation in PF consumption that was accompanied by PF-CPP. Strikingly, the escalation in consumption coincided with an escalating, nearly perfect correlation with PF-CPP ($r = 0.95$), thus assigning increasing motivational value behind each binge episode. The B6NJ strain showed robust binge-like eating that was accompanied by PF-CPP and conditioned locomotor activity whereas the closely related C57BL/6J substrain (B6J) did not show either behavior. Interestingly, B6NJ also showed a three-fold increase in anxiety-like behavior relative to B6J, even prior to palatable food training, supporting the hypothesis that anxiety is a risk factor for binge eating. Importantly, we identified a single genome-wide significant QTL on chromosome 11 that was responsible for differences in both palatable food consumption (LOD = 3.6-5.8; peak = 24-34 Mb) and conditioned food reward (LOD = 4.0; peak = 39 Mb; B6NJ allele > B6NJ allele for both traits). Finally, we identified a second, independent QTL on chromosome 11 (LOD = 3.5; peak marker = 82 Mb) that influenced anxiety-like behavior.
Conclusions: Outbred CFW and inbred B6NJ mice showed binge-like eating and conditioned food reward whereas inbred B6J mice did not. We identified a QTL on chromosome 11 that influenced both the consummatory and motivational properties of palatable food consumption, indicating that binge eating and conditioned food reward are mediated by the same genetic factor(s). Interestingly, nearly the same locus was previously identified for cocaine-induced locomotor sensitization, suggesting a shared genetic basis. The identification of a second locus on chromosome 11 for anxiety-like behavior indicates a separate genetic mechanism. The reduced genetic complexity of this cross will greatly accelerate gene identification.

Future directions include mapping expression QTLs (eQTLs) and using CRISPR/Cas9 to genome edit the candidate, quantitative trait nucleotides. Lastly, we will use outbred CFW mice and other high resolution, genetically diverse mapping populations to enrich our understanding of the genetic architecture of binge eating. Our results could inform translational genetic studies and novel pharmacotherapeutic development for treating binge eating in humans.
Keywords: QTL, GWAS, reward, motivational.
Disclosure: Nothing to Disclose.

W102. Early Life Stress and Psychophysiological Response to Stress During Pregnancy and Postpartum

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Background: In humans, early life stress (ELS) can result in HPA axis dysregulation in adulthood and is a risk factor for psychopathology. History of ELS has been associated with blunted cortisol awakening response during pregnancy. We examined whether ELS impacts HPA axis or autonomic nervous system (ANS) reactivity during pregnancy. Salivary cortisol response, heart rate, and acoustic startle response were assessed as noninvasive measures of HPA axis function and psychophysiology during pregnancy and postpartum. We aimed to determine whether pregnancy alters HPA/ANS response, and whether ELS alters HPA/ANS response. If there is HPA and/or ANS system dysregulation during pregnancy as a function of maternal ELS, this could be transmitted to the fetus through epigenetic and placental factors, which could affect pregnancy and offspring outcomes.
Methods: Women were assessed during pregnancy and postpartum, in a repeated measures design. Women 8-17 weeks gestational age with no SCID diagnoses completed the Adverse Childhood Experience Questionnaire (ACE). Affective modulation of acoustic startle response (ASR) was conducted at 15-21 weeks gestation and was repeated at 15-21 weeks postpartum. Cortisol reactivity to the Trier Social Stress Test (TSST) was measured during pregnancy at 15-21 weeks gestational age. Correlation analyses assessed relationships among ACE, ASR and cortisol response. Paired sample T-tests compared ASR during pregnancy with postpartum, and analysis of variance assessed influence of ACE on this relationship. For some statistical analyses, women were grouped into low ACE (0-1 adverse events) or high ACE (2 or more adverse events).
Results: During pregnancy, 27 women completed ASR and 12 completed TSST. Postpartum, 11 completed ASR. •Baseline startle was not significant different between pregnancy and postpartum ($p = 0.35$). •Heart rate during ASR did not vary significantly between pregnancy and postpartum, and did not vary by ACE status ($p's > 0.05$). •Salivary reactivity was intact during pregnancy after the TSST. Salivary cortisol response (area under the curve; AUC) to the TSST during pregnancy was not correlated with ACE score ($p = 0.85$). •Women exhibited greater mean startle magnitude during postpartum during the unpleasant ($p = 0.05$) affective condition, compared to during pregnancy. There was a trend such that women exhibited greater startle magnitude during postpartum in the pleasant ($p = 0.08$) affective condition compared to pregnancy. •Childhood adversity (ACE) was not significantly correlated with baseline ASR during pregnancy ($p = 0.83$) or postpartum ($p = 0.80$). However, mean baseline ASR increased in magnitude (AU) from 17.9 AU during pregnancy to 56.8 AU postpartum in high ACE women, but remained more stable with ASR of 39.1 AU and 40.9 AU in low ACE women during pregnancy and postpartum, respectively. •Salivary cortisol response (area under the curve; AUC) during the ASR task was positively correlated with ASR magnitude in the unpleasant affective condition ($p = 0.04$) during pregnancy, but not postpartum.
Conclusions: •In this pilot sample, ASR was accentuated during the postpartum compared to pregnancy, in the affectively unpleasant condition. This likely represents a dampening of ASR during pregnancy, as ASR magnitudes in postpartum were consistent with those typical of nonpregnant women. •ASR was not significantly different between low ACE and high ACE groups. While not significant, preliminary data suggests that the increase in ASR from pregnancy to postpartum may be accentuated in women who had experienced childhood adversity.
Keywords: pregnancy, acoustic startle, postpartum, cortisol.
Disclosure: Nothing to Disclose.

W103. Molecular Mechanisms Underlying Marked Elevations in Cortical Immune Markers in Schizophrenia

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Background: Immune- and inflammation-related abnormalities play an important role in the disease process of schizophrenia as indicated by evidence from genome-wide association studies, peripheral serum analyses, and maternal immune activation studies. Interestingly, we recently reported evidence of immune dysfunction in the prefrontal cortex (PFC) in schizophrenia, including higher mRNA levels for the viral restriction factor interferon-induced transmembrane protein (IFITM) which inhibits viral entry processes and replication. However, it is unclear whether higher IFITM mRNA levels in the PFC in schizophrenia are the downstream consequences of 1) ongoing immune activation in the PFC (i.e. higher levels of immune markers that induce IFITM expression), 2) peripheral immune activation, such as higher serum IL-6 levels previously reported in schizophrenia, or 3) a long-lasting maladaptive response to maternal immune activation. To address these questions, we conducted postmortem brain tissue studies of immune markers that regulate IFITM in a large cohort of schizophrenia subjects and in mice exposed to immune stimulation pre- or postnatally.
Methods: Quantitative PCR was employed to measure mRNA levels for immune system cytokines and transcriptional regulators that induce (e.g., interferon-β, IL-6, nuclear factor-κB) or suppress (e.g., Schnurri-2) IFITM

expression in PFC area 9 from 62 schizophrenia and 62 healthy comparison subjects. Normal saline or the immune stimulant poly I:C (20 mg/kg) were injected (IP) daily for 3 days in timed pregnant mice at mid- (E11-13; n = 12) or late-gestation (E15-17; n = 12) and in non-pregnant adult female mice (n = 8). Quantitative PCR was performed for immune markers in the frontal cortex of 8 week old male and female offspring available from each injected mother and the non-pregnant, poly I:C-injected adult mice. All experimental procedures follow requirements listed in the NIH Guide for the Care and Use of Laboratory Animals and have been approved by the University of Pittsburgh IACUC and Division of Environmental Health and Safety.

Results: Initial analysis of schizophrenia subjects revealed markedly higher mRNA levels for cytokines and transcription factors that induce IFITM expression, including IL-6 (+380%), interferon-β (+30%), and nuclear factor-κB (+86%), and lower mRNA levels for Schnurri-2 (-10%), a nuclear factor-κB site-binding protein which suppresses cytokine production, in the PFC (for all, $p < .05$). Furthermore, IFITM mRNA levels were positively correlated with mRNA levels for IL-6 ($r = 0.26$), interferon-β ($r = 0.25$), nuclear factor-κB ($r = 0.73$,) and negatively correlated with Schnurri-2 mRNA levels ($r = -0.32$) (for all, $p < .05$). Interestingly, frontal cortex mRNA levels for IFITM (+304%) and IL-6 (+493%) were also markedly elevated in adult female mice that received daily poly I:C injections ($p < .05$), but not in the young adult offspring of poly I:C-injected mothers.

Conclusions: Our findings suggest that higher IFITM mRNA levels in the PFC in schizophrenia may be attributable to 1) markedly higher levels of cytokines and transcription factors that induce, and lower mRNA levels for a nuclear factor-κB site-binding protein that inhibits, IFITM expression in the PFC and/or 2) peripheral immune activation as supported by the results of acute/subacute administration of poly I:C to adult mice, but not 3) exposure to maternal immune activation in mid- or late gestation. The striking magnitude of cortical immune activation in schizophrenia may lead to deleterious effects on cortical circuitry (or perhaps vice versa) and indicate that immune-related markers may serve as therapeutic targets in the disorder.

Keywords: schizophrenia, immune, maternal immune activation, prefrontal cortex.

Disclosure: David A. Lewis currently receives investigator-initiated research support from Bristol-Myers Squibb and Pfizer. All other authors have no disclosures to report.

W104. The Somatostatin Promoter is Hypermethylated in the Aged Human Prefrontal Cortex

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Background: Somatostatin (SST) expression in the human prefrontal cortex exhibits a progressive decrease with aging. Though decreased SST expression in the prefrontal cortex of individuals of advanced age has been consistently demonstrated, the mechanism by which this decrease in expression occurs is unknown. Here, we investigate the contribution of DNA methylation to the regulation of SST expression in aging.

Methods: Genomic DNA was prepared from the prefrontal cortices (areas BA11 and BA47) of postmortem brains from twenty younger individuals (age < 40) and twenty older individuals (age > 60), the older group was enriched for individuals exhibiting particularly low levels of SST expression. Genomic DNA was then treated with sodium bisulfite and bisulfite-specific PCR amplification was performed on of the 5' region of SST in a real-time thermocycler. The amplified bisulfite modified DNA was then heated and the temperature at which half the amplicon melted (T50) calculated using fluorescence data from the theromcycler.

Results: The T50 of amplicons produced from older individuals is significantly higher compared to the T50 from younger individuals.

Conclusions: The 5' region including areas surrounding the transcriptional start site, first exon, and intron of SST is hypermethylated in DNA isolated from the prefrontal cortex of individuals of advanced age suggesting that DNA hypermethylation may contribute to the low levels of SST expression observed in the brains of older individuals. Because expression of SST is decreased in the brains of individuals with advanced age, understanding how SST expression is regulated in the brain is critical to understanding the pathology of brain aging and developing interventions to prevent and treat brain aging. This study suggests that DNA methylation may be one mechanism by which SST expression is regulated in the aging human brain.

Keywords: Somatostatin, DNA Methylation, Aging, Prefrontal Cortex.

Disclosure: Nothing to Disclose.

W105. Human MDMA (Ecstasy; Molly) Users have Increased Cortical Excitability

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Background: MDMA, a drug that has well-demonstrated serotonin (5HT) neurotoxic effects in rodents and non-human primates, is widely used by young adults. Recreational MDMA polydrug use is associated with increased risk for depression, anxiety, and suicide attempts. Results from our ongoing MDMA research program have previously demonstrated that MDMA use is associated with chronic and specific shifts in brain neurophysiology and 5HT function. Our prior fMRI studies found that MDMA use is associated with increased activation during motor and visual tasks, results consistent with increased cortical excitability. Nuclear imaging studies of the 5HT reuptake transporter and the 5HT2A receptor suggest that reduced 5HT signaling may underlie the observed shifts in brain activation and neurophysiology. The basic neuroscience of 5HT physiology suggests that reduced 5HT would lead to an increase in cortical excitability and chronic MDMA increases cortical excitability in mice. Multiple reports from our lab group found that MDMA use is associated with

increased stimulus-evoked activation—a result strongly suggestive of increased cortical excitability. We used transcranial magnetic stimulation (TMS) of visual and motor cortex to directly assess the cortical excitability threshold in abstinent MDMA users and controls.
Methods: We enrolled male and female MDMA (N = 12) users and controls (n = 8) whose mean age was 22 (± 3.02) years. MDMA users self-reported abstinence from all drugs for at least 2 weeks. TMS was administered with a Magstim 2T Rapid stimulator (Magstim Company, UK; peak discharge = 1.8 kV; 70-mm figure-eight). The TMS coil was stereotactically positioned using each participant's T1-weighted structural MRI acquired prior to the stimulation procedure. We positioned the coil independently for each subject, to allow evocation of the phosphene within 2° of the fovea; coil location was about 2 cm above the inion. A binary search paradigm established the TMS intensity threshold at which each observer reported a motor twitch or phosphene on 75% of stimulations. Coil position yielding a phosphene was localized with eyes closed, and the coil was set at 90% intensity. TMS intensity is then set to 54% intensity and adjusted until the individual is able to detect the threshold on 75% of trials of the given intensity.
Results: The MDMA user group (N = 12) reported median MDMA use of 12.00 (min = 5 max = 40) episodes, with median consumption of 1000.00 (min = 250 max = 6000) mg. The average duration of abstinence since last MDMA use was 203.50 (min = 31 max = 996) days. TMS threshold for both visual and motor regions was significantly lower in the MDMA user group. For visual phosphene generation, the mean threshold was 65.45% (± 6.50%) for MDMA users and 80.71% ± (6.73%) in the control group (Independent samples T test; $p < 0.001$). For motor twitch, the mean threshold was 65.83% (± 7.64%) for the MDMA users and 76.88 (± 5.30%) for the controls ($p = 0.002$). In addition to the between groups differences in TMS threshold, within the MDMA group lifetime MDMA exposure and abstinence duration were inversely associated with visual TMS threshold (episodes: rs = -.86, $p < 0.001$; consumption: rs = -.77, $p = 0.006$; abstinence duration: rs = -.77, $p = 0.006$). No statistically significant associations of MDMA exposure or abstinence duration were observed for motor stimulation (largest duration: rs = -.50, $p = 0.102$).
Conclusions: Based on our earlier BOLD fMRI findings of increased activation in visual and motor cortices in MDMA users and upon the primarily inhibitory role for serotonin in cortex, we predicted that MDMA users would have increased cortical excitability (lower TMS threshold) in visual and motor regions as measured with TMS and that lifetime MDMA consumption would be inversely associated with TMS threshold. Our preliminary findings largely support these predictions. In addition, we found no evidence that these differences were reduced with sustained abstinence. These findings are consistent with the predicted consequences of chronic reductions in serotonin signaling and align with a broad range of findings from other modalities in human recreational MDMA users that suggest that MDMA produces long-lasting serotonergic axon toxicity in the cortex.
Keywords: MDMA, serotonin, cortical excitability, transcranial magnetic stimulation.
Disclosure: Nothing to Disclose.

W106. Predicting Response to Antipsychotics with Proton Magnetic Resonance Spectroscopy (MRS)

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Background: Prediction of response to antipsychotic treatment based on biomarkers is an important goal, both for clinical decision making with currently available medications and for assessing the potential efficacy of medications with new mechanisms of action. Here we used MRS in the anterior cingulate/medial prefrontal cortex (ACC) during a period of suspension of all neurotropic medication in patients with psychosis to predict short-term clinical response to antipsychotics. Others have reported higher levels of metabolites indexing glutamatergic metabolism (Glx, a metabolite peak composed of glutamate, glutamine and GABA, or glutamate itself) in patients who are poor responders to antipsychotics as compared to those who respond more robustly. Szulc et al. (2013) scanned chronic patients after a washout period of 7-14 days and found lower Glx levels in those who showed an improvement in symptoms of at least 20% after 4 weeks of antipsychotic treatment against those who did not reach this criterion. Egerton et al. (2012) demonstrated increased glutamate levels in first episode patients who still had more than mild symptoms compared to those who had only mild or no symptoms after a full course of treatment. We predicted that higher Glx levels after a period of neuroleptic suspension of at least 14 days would be associated with poorer symptom response, especially for positive symptoms, which are more likely to respond to current antipsychotic agents. The MRS sequence we used allowed us to measure GABA in addition to glutamate. This metabolite has never been studied as a predictor of response to antipsychotics, to our knowledge.
Methods: 15 patients with psychosis (11 with schizophrenia, 2 with schizoaffective disorder and 2 with psychosis NOS; 6 females; ages 21 -55, mean 28.4 + 9.5 SD; illness duration 0.5-31 years, mean 8.2 + 8.3 SD) participated in double blind cross-over design where all medications were suspended for 4-6 weeks (placebo phase) or a single antipsychotic was administered at a stable dose (active phase: 8 patients on risperidone, 3 on aripiprazole, 2 on olanzapine, one on ziprasidone and one on quetiapine). The order of treatment phases was placebo first in 5 patients, active first in 10. Trained nurses collected the positive and negative symptoms scale (PANSS) twice a week, blind to the medication status of the patients. MRS (a sequence optimized for detection of GABA via j-editing at 3T, with a single voxel placed in the ACC) was performed after at least 2 weeks during the placebo and the active phase. We report only the values for the first scan. The metabolite values N-acetyl-aspartate (NAA, containing also N-acetyl-aspartyl-glutamate), GABA, and Glx, all referenced to creatine, were used as independent variables in multiple regression models predicting change in PANSS score between the first and second scan while controlling for age and sex. Change in PANSS score was measured as 1) the average score across all 30 items of the positive and negative

symptoms scale (PANSS) or as 2) the average of positive symptoms only.
Results: Glx/Cre in the ACC was significantly negatively associated with change in positive symptoms ($p < 0.007$, the higher the Glx/Cre the lower the difference in PANSS between placebo and active phases). No other metabolite ratio was significantly associated with antipsychotic response for either overall symptoms or positive symptoms. This relationship also was present when analyzing Glx referenced to water and was absent for creatine/water.
Conclusions: These preliminary data seem to support the presence of higher glutamate related metabolites in patients with lesser response to antipsychotics. Egerton et al. (2012) suggested that patients with higher glutamate levels might require medications with a different mechanism of action from currently available dopaminergic drugs. GABA did not appear to be predictive of antipsychotic response. Larger groups of patients are needed to confirm these findings.
Keywords: schizophrenia, glutamate, PANSS, GABA.
Disclosure: Nothing to Disclose.

W107. Expression of MIR132 and MIR137 in Postmortem Human Prefrontal Cortex of Patients with Schizophrenia and Non-psychiatric Controls

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Background: MicroRNAs (MIRs), small non-coding RNAs, can regulate stability and translation of multiple mRNAs, and affect multiple biological pathways and brain development. Several MIRs have been recently implicated in schizophrenia, including MIR132 and MIR137. MIR132 was shown to be dysregulated in schizophrenia in two postmortem studies, although the direction of changes was inconsistent. MIR137 was identified through a large genome-wide association study, which found that rs1625579, located in the intronic region of MIR137 host gene, was strongly associated with schizophrenia. In subsequent studies, a risk-associated common allele (T) was shown to predict the severity of cognitive deficits in schizophrenia, regional brain activity, and changes in brain structure. In this study, we attempted to clarify changes in MIR132 expression using a large cohort of patients and controls, and investigate whether MIR137 expression is associated with rs1625579 and altered in schizophrenia.
Methods: We measured expression of MIR132 and MIR137 in the dorsolateral prefrontal cortex (DLPFC) of 286 subjects (198 controls and 88 patients with schizophrenia), ranging in age from birth through old age (over 80 years old). We also determined the effects of rs1625579 on MIR137 expression. RNA was extracted using miRNeasy Kit (QIAGEN). Reverse transcription was conducted using specific miRNA primers (ABI). TaqMan qPCR assays measured MIR132-5p and MIR132-3p as well as MIR137 expression levels, which were then normalized to a geometric mean of U6 and U44 small nucleolar RNA (snoRNA). The genotypes at rs1625579 were obtained using Illumina BeadArrays (1M). We used analysis of covariance (ANCOVA) with diagnosis as a categorical variable, and age, sex, pH, postmortem interval (PMI) and RNA integrity (RIN) as covariates. For MIR137 we also conducted ANCOVA with diagnosis and genotype at rs1625579 as well as race (157 African Americans and 71 Caucasians) and genotype as independent variables.
Results: DLPFC expression of MIR132-5p and MIR132-3p did not differ between patients with schizophrenia and controls (ANCOVA: $F = 0.16$, $p > 0.5$). Expression of both MIR132 subtypes was negatively correlated with age with highest levels detected at birth ($r = -0.5$, $p < 0.001$). Expression of MIR137 also decreased with age throughout the lifespan ($r = -0.35$, $p < 0.001$). There was no significant effect of genotype at rs1625579 on MIR137 expression in all subjects ($F = 0.3$, $p = 0.7$) and separately in controls ($F = 1.5$, $p = 0.2$). There was also no significant effect of diagnosis ($F = 0.08$, $p = 0.8$) and genotype ($F = 0.3$, $p = 0.7$) on expression of MIR137, and no significant genotype by diagnosis interaction. Moreover, we did not detect a significant effect of race or genotype at rs1625579, and there was no race by genotype interaction on MIR137 mRNA expression ($F = 0.3$, $p = 0.8$).
Conclusions: In conclusion, we did not find differences in MIR132 and MIR137 expression between controls and patients with schizophrenia or a significant effect of genotype at rs1625579 on MIR137 expression in the DLPFC in our large dataset. The molecular mechanisms underlying clinical association with schizophrenia remain elusive.
Keywords: miRNAs, prefrontal cortex, schizophrenia, expression.
Disclosure: Nothing to Disclose.

W108. Chondroitin Sulfate Proteoglycan Abnormalities in Schizophrenia: Involvement of NG2 (nerve/glial Antigen 2 - CSPG4)

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Background: Growing evidence points to an involvement of chondroitin sulfate proteoglycans (CSPGs) in the pathophysiology of schizophrenia (SZ). CSPGs are one of the main components of the extracellular matrix, and are also expressed on the cell surface of distinct glial and neuronal cells. In the amygdala and entorhinal cortex of subjects with SZ, we have shown marked decreases of CSPG-enriched pericellular extracellular matrix aggregates, i.e. perineuronal nets, accompanied by altered CSPG expression in glial cells. Several CSPGs are involved in these abnormalities, including aggrecan, CSPGs carrying a distinct pattern of sulfation (CS-6), and those labeled with the lectin wisteria floribunda agglutinin (WFA). Glial cells labeled with this latter marker were sharply increased in SZ. We recently found that a subset of these WFA-labeled glia is closely associated with myelinated axon bundles and expresses NG2, a selective marker for oligodendrocyte progenitor cells (OPCs). This finding raises the intriguing possibility that OPCs may be involved in the pathophysiology of SZ.
Methods: OPCs are the main source of mature oligodendrocytes in adult brain, dynamically regulating the pool of myelinating oligodendrocytes. In addition, they are active components of the neuron/glia synaptic complex and nodes of Ranvier, and are thus involved in synaptic function and axonal conductance. Therefore, abnormalities affecting these

cells may contribute to synaptic, myelination and connectivity abnormalities reported in SZ. Notably, NG2 is itself a CSPG, also known as CSPG4, exclusively expressed on the surface of OPCs. With the present studies, we tested the hypothesis that CSPG abnormalities in SZ may include altered NG2 expression in the amygdala of subjects with SZ. Postmortem tissue blocks containing the amygdala from normal control (n = 11) and SZ (n = 15) subjects were obtained from the Harvard Brain Tissue Resource Center. Serial sections were processed for immunocytochemistry using an antibody raised against NG2. Numbers of NG2-immunoreactive (IR) glial cells in the lateral (LN), basal (BN), accessory basal (ABN), cortical (CO), medial (ME) and central (CE) nuclei of the amygdala were quantified according to stereology-based methods using computer-assisted light microscopy. The LN from a separate subject cohort (normal control, n = 13; SZ, n = 14) was processed for qRT-PCR to measure NG2 mRNA. Step-wise ANCOVA testing was carried out accounting for several potential covariates, including pharmacological treatment and substance abuse. Effect sizes were calculated according Hedges' g.

Results: NG2 mRNA was significantly increased in the LN of subjects with SZ ($p = 0.0001$, $g = 2.32$). In contrast, total numbers and numerical densities of NG2-IR glia were significantly decreased in the amygdala of subjects with SZ (p and g values provided for total numbers): LN, $p = 0.02$, $g = -1.25$; BN, $p = 0.005$, $g = -1.69$; ABN, $p = 0.05$, $g = -1.1$; CO, $p = 0.01$, $g = -1.38$; CE, $p = 0.009$, $g = -1.53$. In the ME, decreases did not reach significance ($p = 0.06$, $g = -1.03$). Notably, significance values were corrected for exposure to valproic acid, which showed a significant effect on total numbers and numerical densities (p values ranging between 0.01 – 0.001), and was significantly, and positively, correlated with total numbers and numerical densities of NG2-IR glia in subjects with SZ ($p < 0.01$). The strong effects of valproic acid on NG2 expression, supported by animal models showing similar effects, was reflected in a sharp dichotomous clustering of subjects, with those exposed to this drug showing high numbers of NG2 cells, while those that were not exposed clustered well below the healthy control mean. Interestingly, all subjects exposed to valproic acid were reported to have significant affect disturbances, raising the possibility that the dichotomous distribution observed may instead be related to symptom presentation along the SZ spectrum.

Conclusions: Our results show a significant decrease of numbers of NG2-IR OPCs in the amygdala of subjects with SZ. Increased NG2 mRNA expression, possibly due to translational abnormalities, suggests that numbers of OPCs may not, in themselves, be lower. Instead, expression of NG2 in these cells may be decreased. This interpretation will be corroborated by further studies, but is consistent with current findings showing changes of CSPG expression in glial cells in absence of altered numbers of glial cells. Marked decreases of NG2-IR OPCs in subjects with SZ point to a pathology of these cells in the amygdala. We put forth that OPC abnormalities in SZ may profoundly compromise the supply of mature oligodendrocytes, and disrupt synaptic functions, myelination and impulse transmission. VPA may contribute to alleviate these abnormalities.

Keywords: schizophrenia, postmortem, NG2, chondroitin sulfated proteoglicans.

Disclosure: Nothing to Disclose.

W109. Proinflammatory Cytokines and Their Receptors in the Depressed Suicide Brain

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Background: Abnormalities of the immune system in the pathogenesis of depression have been suggested by several investigators. The major evidence to support abnormalities of immune function in depression is derived from the studies of cytokines which are generally known as chemical messengers between immune cells and comprise a heterogeneous group of messenger molecules. That cytokines might play an important role in depression has been substantiated by the observation that administration of cytokines such as IFN-α to cancer patients causes symptoms known as sickness behavior which is very similar to depression, and that the levels of proinflammatory cytokines and their soluble receptors are increased in the serum of depressed patients. Both depression and stress are major risk factors for suicidal behavior and, therefore, it is not surprising that abnormal immune function has also been implicated in suicide. Some recent studies suggest that the levels of IL-6 and TNF-α in the CSF of suicide attempters are higher as compared to normal control subjects. Cytokines are involved in a bi-directional signaling between the central nervous system (CNS) and the peripheral immune system. Cytokines and their receptors have been shown to be present in the brain. Whereas cytokines and their soluble receptors have been studied in the serum of patients, the cytokines and their membrane bound receptors have not been studied in the brain of depressed or suicidal subjects. The physiological function of cytokines is mediated through membrane bound receptors which initiate cellular signaling resulting in a functional response. We have, therefore, studied proinflammatory cytokines and their membrane bound receptors in the PFC of depressed suicide subjects. Although there are some studies of cytokines in the CSF of suicidal and depressed patients, the role of cytokines in the brain is not clear. We reported that the levels of proinflammatory cytokines, IL-1β, IL-6 and TNF-α, are increased.

Methods: Postmortem brain samples were obtained from the Maryland Brain Collection at the Maryland Psychiatric Research Center, Baltimore, MD. The cytokines and their receptors were determined in the prefrontal cortex of 24 normal control subjects and 24 depressed suicide victims. All subjects were diagnosed using the Schedule for Clinical Interviews for the DSM-IV (SCID). All procedures were approved by the Institutional Review Board of the University of Maryland. Determination of the proinflammatory cytokine levels was performed by the ELISA method using quantakine kits from R&D Systems, Minneapolis, MD. The protein expression levels of the membrane-bound cytokine receptors were determined using the Western blot technique.

Results: There was no difference in the mean age, mean postmortem interval (PMI), or pH between normal control subjects and depressed suicide subjects. We compared the protein expression levels of IL-1β, IL-6 and TNF-α between suicide subjects and normal control subjects and found that the protein expression level of

IL-1β, IL-6 and TNF-α was significantly higher in the prefrontal cortex of suicide victims compared to normal control subjects. When we compared the protein expression levels of the receptor subtypes for the proinflammatory cytokines we found that the protein expression levels of the receptors IL-1R1, IL-1R2 and IL-1R antagonist (IL1RA) were significantly lower in the prefrontal cortex of suicide victims compared to normal control subjects. We also found a significant decrease in Gp130 as well as TNF-R1 and TNF-R2 in the prefrontal cortex of depressed suicide victims compared to normal control subjects. However, there was no significant difference in the protein expression levels of IL-6Rα between depressed suicide victims and normal control subjects.

Conclusions: This study demonstrated that the protein expression of proinflammatory cytokines and their receptors are abnormally expressed in the PFC of depressed suicide victims compared to normal control subjects. Our study thus suggests that abnormalities of proinflammatory cytokines and their membrane bound receptors are associated with the pathophysiology of depression and suicide.

Keywords: Depression, Suicide, Cytokines, Inflammatory Markers.

Disclosure: Nothing to Disclose.

W110. Effects of Acute Tryptophan Depletion and Phenylalanine-Tyrosine Depletion on Bimodal Divided Attention in Healthy Adult Volunteers

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Background: The interplay of dopamine (DA) and serotonin (5-HT) in attentional performance has been the subject of many studies. Impairments in this particular cognitive domain are often found in patients with psychiatric disorders which are thought to be related to dysfunctions in these neurotransmitter systems. The present study aimed to explore the effects of a short-term reduction in central nervous synthesis of DA and 5-HT on bimodal divided attention. A novel acute phenylalanine-tyrosine depletion (APTD) technique as well as established acute tryptophan depletion protocol (ATD) and a balanced amino acid control mixture (BAL) were administered to healthy participants who were subjected to a test on bimodal divided attention (auditory/visual) after challenge intake.

Methods: After a 12-hour protein-fast, 54 healthy adult participants (age: $M = 23.8$ $SD = 4.6$) received a standardized low protein breakfast before being randomly assigned to one of the challenge conditions in a double-blind, between-subject approach (APTD $N = 17$; ATD $N = 16$; BAL $N = 16$). A bimodal divided attention task was applied 4 hours after challenge intake as part of a larger battery of different behavioural tasks and neuropsychological tests. Blood samples for analysis of amino acid levels were taken before and 6 hours after challenge intake.

Results: Changes in amino acid concentrations in the blood after challenge intake were in the expected direction (decrease) and were found to be significant (all $p \leq .01$). A one-way ANOVA indicated a significant difference in the mean reaction time (RT) towards auditory stimuli but not towards visual stimuli between the challenge groups in the used divided attention task. A Bonferoni post-hoc comparison of the mean RT to auditory stimuli showed a significant difference between ATD ($RT = 604.0$ ms, $SD = 56.9$ ms) and APTD ($RT = 556.4$ ms, $SD = 54.2$ ms; $p = .037$) administration, but no difference in RT between ATD and BAL or APTD and BAL administration ($RT = 573.6$ ms, $SD = 45.7$ ms).

Conclusions: The results of the present pilot study indicate a possible dissociation between the effects of a short-term diminished central nervous 5-HT and DA synthesis on the performance in a bimodal divided attention task in healthy subjects. In particular, the found difference was exclusively observed within the RT towards auditory signals. With respect to the critical role of serotonergic projections within the auditory system from the cochlea to the cortex, diminished availability of 5-HT may impair intact auditory processing and gating in the context of a complex attentional task, whereas reduced tonic DA-related activity has been linked to an improved attentional control. Regarding the complex nature of the monoaminergic system, further research is necessary to disentangle the interactions of 5-HT and DA in the context of divided attention.

Keywords: Attention, Serotonin, Dopamine, monoamine depletion.

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W111. Imaging Neuroinflammation in Gray and White Matter in Schizophrenia: An in-Vivo PET Study with [18F]-FEPPA

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Background: Neuroinflammation and abnormal immune responses have been implicated in schizophrenia. Past studies using positron emission tomography (PET) that examined neuroinflammation in patients with schizophrenia in-vivo using the translocator protein 18 kDa (TSPO) target were limited by the insensitivity of the first-generation imaging agent [11C]-PK11195, scanners used, and the small sample sizes studied. Present study uses a novel second generation TSPO PET radioligand [18F]-FEPPA to evaluate whether there is increased neuroinflammation in patients with schizophrenia.
Methods: A cross-sectional study was performed using [18F]-FEPPA and a high resolution imaging tomograph (HRRT). Eighteen patients with schizophrenia with ongoing psychotic symptoms and 27 healthy volunteers were recruited from a tertiary psychiatric clinical setting and the community, respectively. All participants underwent [18F]-FEPPA PET and MRI imaging, and PET data were analyzed to obtain [18F]-FEPPA total volume of distribution (VT) using a two-tissue compartment model with an arterial plasma input function, as previously validated. All subjects were classified as high-, medium- or low-affinity [18F]-FEPPA binders on the basis of rs6971 polymorphism, and genotype information was incorporated into the analyses of imaging outcomes.
Results: No significant differences in neuroinflammation indexed as [18F]-FEPPA VT were observed between groups in either gray ($F(1,39) = 0.179$, $p = 0.674$) or white matter regions ($F(1,38) = 0.597$, $p = 0.445$). No significant associations (bonferroni corrected) were found.
Conclusions: The lack of significant difference in neuroinflammation in treated patients with schizophrenia in the midst of a psychotic episode and healthy volunteers suggests that neuroinflammatory processes may take place early in disease progression, or are affected by antipsychotic treatment.
Keywords: neuroinflmmation, microglia, psychosis, PET.
Disclosure: Nothing to Disclose.

W112. Decreased Calretinin/Glutamic Acid Decarboxylase 67 Immunoreactive Boutons in the Prefrontal Cortex of Subjects with Schizophrenia

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Background: Convergent findings indicate that cortical GABA circuitry is altered in schizophrenia. GAD65 and GAD67 catalyze the synthesis of GABA within synaptic boutons. Deficits in GAD67 mRNA and protein, but not in GAD65, have been consistently found in the prefrontal cortex (PFC) of schizophrenia subjects. GAD67 mRNA levels are markedly reduced in ~30% of neurons but are not different from control values in the remaining GABAergic neurons, suggesting that a specific subpopulation(s) is affected in schizophrenia. GABAergic neurons that express calretinin (CR+), parvalbumin (PV+), or calbindin (CB+) are non-overlapping subtypes that constitute ~45%, 25%, and 20%, respectively, of all GABAergic neurons in primate PFC. In schizophrenia, ~50% of PV mRNA-positive neurons lack detectable levels of GAD67 mRNA and GAD67 protein levels are significantly lower in PV+ basket cell boutons. Thus, PV+ neurons with undetectable levels of GAD67 mRNA account for ~1/3 of the neurons in which GAD67 is markedly reduced. In schizophrenia, mRNA levels of somatostatin (SST), which is expressed by a subset of CB+ neurons, are lower. Lower SST mRNA correlates with lower GAD67 mRNA levels, suggesting GAD67 might be lower in a subset of CB+ neurons. In contrast, CR levels are unchanged and do not correlate with GAD67 levels, suggesting CR+ neurons are unaltered. To test the hypothesis (H1) GAD67 levels are reduced in CB+, but not in CR+, GABAergic neurons we used quantitative fluorescence microscopy to measure the GAD content of boutons arising from these two cell types in the PFC of subjects with schizophrenia. Importantly, boutons arising from CB+ and CR+ GABAergic neurons can be classified as containing detectable levels of only GAD65 (GAD65+), only GAD67 (GAD67+), or both GADs (GAD65/67+). Thus, we also hypothesized (H2) that the density of CB+/GAD67+ boutons is lower in schizophrenia subjects compared to matched controls, while the density of CR+/GAD67+ boutons does not differ between groups.
Methods: PFC tissue sections from 20 matched pairs of schizophrenia and comparison subjects were quadruple-labeled for GAD65, GAD67, vesicular GABA transporter (vGAT), and CB or CR immunoreactivity. Quantitative immunofluorescence microscopy techniques were then used to assess the density of CB+ and CR+ boutons, and relative GAD protein levels within these boutons. Post image capture, custom threshold/morphological segmentation algorithms were used to identify CB+ and CR+ GABAergic (vGAT+) boutons, which were then classified as being GAD65+, GAD67+, or GAD65/67+.
Results: (H1) In subjects with schizophrenia, across all layers relative GAD67 protein levels were significantly 13% lower in CB boutons and unchanged in CR boutons. In addition, relative CB protein levels within boutons were significantly 13% lower, while CR bouton protein levels were unchanged. (H2) Across all layers vGAT-GAD (GAD65+ and/or GAD67+) bouton density was significantly 7% lower in schizophrenia subjects compared to controls. GAD67+ boutons that contained no detectable GAD65 were significantly 24% lower in subjects with schizophrenia compared to controls. The lower density of vGAT+/GAD67+ boutons was in part due to a significantly 22% lower CR+/vGAT+/GAD67+ bouton density. In contrast, CB+/vGAT+/GAD67+ bouton density was unchanged.
Conclusions: In concert, the findings confirmed the first half of H1, GAD67 levels are reduced in CB+ GABAergic

neurons; however, they rejected the second half, GAD67 levels are not reduced in CR + neurons. In addition, they rejected H2, the density of CB + /vGAT + /GAD67 + boutons, but not CR + /vGAT + /GAD67 + boutons, is lower in schizophrenia. Furthermore, the findings suggest that CB + neurons do not contribute to the population of GABAergic neurons with undetectable levels of GAD67 mRNA in schizophrenia. However, the reductions in GAD67 within CB + boutons would presumably result in decreased inhibition from these neurons in schizophrenia. In contrast, the finding that the density of CR + /vGAT + /GAD67 + boutons was lower in schizophrenia suggests that GAD67 mRNA is markedly reduced in at least a subpopulation of CR + neurons. CR + neurons mostly synapse onto other inhibitory neurons. Thus, the finding that the CR + /vGAT + /GAD67 + bouton density was significantly reduced in schizophrenia might reflect either a primary GABA deficit in non-CR + GABAergic neurons (e.g., PV +) such that the changes detected here are compensatory, or a primary deficit in CR + GABAergic neurons.

Keywords: calretinin, calbindin, GABAergic boutons, GAD.

Disclosure: David A. Lewis currently receives investigator-initiated research support from Bristol-Myers Squibb and Pfizer and in 2012-2014 served as a consultant in the areas of target identification and validation and new compound development to Autifony, Bristol-Myers Squibb, Concert Pharmaceuticals, and Sunovion.

W113. Poor Sleep Quality as a Vulnerability Factor for Inflammation-induced Depressive Symptoms in Women

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Background: Sleep disturbance and depression are major public health burdens, particularly in women, and sleep disturbance is a well-known risk factor for depression. Systemic inflammation has been suggested as a potential mechanism of this association. This study examined whether self-reported poor sleep quality acted as a vulnerability factor for inflammation-induced depressive symptoms among healthy women.

Methods: Healthy female participants aged 18 to 50 ($N = 53$) were randomly assigned to receive either placebo or low-dose endotoxin, which increases proinflammatory cytokine levels in a safe manner. Self-reported depressive symptoms were repeatedly assessed at baseline and over 6 hours after drug administration. In order to examine whether sleep quality moderates the effect of endotoxin on depressive symptoms, the participants were stratified into subgroups with poor vs. good sleep quality by the use of median split of the Pittsburgh Sleep Quality Index global score (≥ 3 vs. < 3).

Results: Participants exposed to endotoxin, compared with placebo, showed greater increases in self-reported depressive symptoms over time. In the subgroup with poor sleep quality, there was a robust time-by-condition interaction ($\chi 2 = 37.60$, $df = 6$, $P < 0.0001$) using mixed-effects model regression. However, in the subgroup with good sleep quality, there was no significant time-by-condition interaction ($\chi 2 = 0.57$, $df = 6$, $P = 0.997$). Formal moderation test was statistically significant even after controlling for age, body-mass index, and baseline depressive symptoms ($\chi 2 = 30.40$, $df = 6$, $P < 0.0001$).

Conclusions: The effect of experimentally-induced systemic inflammation on depressive symptoms was considerably stronger among healthy female subjects reporting poor sleep quality compared to those reporting good sleep quality. Sleep disturbance may increase the vulnerability to the effect of systemic inflammation on depressive symptoms.

Keywords: sleep disturbance, depressive symptoms, systemic inflammation, endotoxin.

Disclosure: Nothing to Disclose.

W114. Decreased Glutamate Concentrations in Anterior Cingulate in Schizophrenia

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Background: Convergent lines of evidence indicate that schizophrenia involves alterations in glutamate neurotransmission. While human postmortem and animal-model studies have been critical in achieving this understanding, any definitive testing of existing models requires in vivo demonstration in humans of neurotransmitter system pathology. In this study we aimed to measure glutamate-related neurochemical profiles in schizophrenia using proton magnetic resonance spectroscopy (MRS) at 7 T, taking advantage of the high field benefits of signal gain and spectral resolution enhancement. The concentrations of glutamate were measured in the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC), two regions critically involved in the pathophysiology of the disease, both in medicated volunteers with schizophrenia (SZ) and normal controls (NC).

Methods: Scanning included a scout scan and several spectral acquisitions with a region of interest focused on the anterior cingulate and dorsolateral prefrontal cortex. For each region, an optimized PRESS scan was conducted at 7T: PRESS (TE1, TE2) = (31, 61) ms for measurement of glutamate, glutamine, NAAG, NAA, creatine, and choline. MRS data acquisition parameters included $TR = 2.5$ s, $Nave = 256$, sweep width = 5 kHz, and number of sampling points = 4096 (scan time $\approx$ 10 min).

Results: Preliminary results from a sample of $N = 14$ normal volunteers and $N = 25$ volunteers with schizophrenia indicated lower glutamate in the anterior cingulate cortex of volunteers with schizophrenia (NC: 1.1 ± 0.06; SZ: 1.056 ± 0.1; $p = 0.01$) and no significant difference between the groups in the levels of DLPFC glutamate.

Conclusions: These preliminary results are consistent with previous reports of the levels of neurometabilites in schizophrenia. We intend to expand the sample by scanning additional participants, as well as unmedicated schizophrenia volunteers.

Keywords: glutamate, MRS, schizophrenia.

Disclosure: Dr Tamminga is or has been a deputy editor for the American Psychiatric Association; an ad hoc consultant for Astellas, Eli Lilly and Lundbeck; a council member for the Brain & Behavior Research Foundation, the Institute of Medicine, the National Alliance on Mental Illness and the National Institute of Mental Health; an organizer for the International Congress on Schizophrenia Research; a consultant for Kaye Scholer; and a member of the advisory board of drug development for Intra-Cellular Therapies. The other authors declare no conflict of interest.

W115. Evidence of Alterations in Brain Metabolites Indicating Neuroinflammatory Responses in Emerging Adult Binge Drinkers

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Background: Binge alcohol consumption is associated with multiple neurobiological consequences, including altered neurophysiology, brain structure and functional activation. Magnetic resonance spectroscopy (MRS) studies have demonstrated abnormalities on the cellular level, in brain chemicals that serve as markers of cellular health and energy in heavy alcohol users, and in individuals with alcohol abuse and dependence.
Methods: In the current study, proton metabolite data were acquired using 2D J-PRESS at 4 Tesla and compared between 18-24 year old binge alcohol drinkers (BD: $n = 23$, 11 female) and light alcohol drinkers (LD: $n = 29$, 15 female). Proton metabolite levels were calculated as ratios to creatine.
Results: BD exhibited significantly higher glutamate ($p = .034$), glutathione (GSH, $p = .027$), myo-Inositol (mI, $p = .047$) and lactate ($p = .041$) in the anterior cingulate cortex (ACC) region of the frontal lobe as compared to LD. No group differences were observed for these metabolites in the parietal-occipital cortex (POC). There also were no significant differences observed for choline, glutamine or NAA levels in either region, with the exception of lower NAA in the POC of BD relative to LD.
Conclusions: Alterations in glutamate may reflect prolonged facilitation of this neuronal target site of alcohol action, whereas reduced NAA may reflect reduced neuronal health. Higher GSH, mI and lactate levels may reflect detoxification and associated neuroinflammatory responses that may accompany a binge pattern of alcohol consumption. These preliminary data suggest that binge drinking compromises neurochemistry, with a heightened vulnerability evident in the ACC region of the frontal lobe. Characterization of neurochemical profiles associated with binge alcohol consumption may help identify unique risk factors for the later manifestation of alcohol abuse and dependence, in young individuals who are heavy, frequent drinkers, but who do not currently meet the criteria for alcohol dependence.
Keywords: neuroinflammation, binge drinking, anterior cingulate cortex, magnetic resonance spectroscopy.
Disclosure: Nothing to Disclose.

W116. Does Myoinositol Level Measured on Proton Magnetic Resonance Spectroscopy Reflect Micorglial or Astroglial Activation?

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Background: Myoinositol is one of the major brain metabolites measured with in vivo proton magnetic resonance spectroscopy (1H MRS). It is a putative glial marker since its concentration is high in astrocytic cell cultures, and is often elevated in conditions known to be associated with neuroinflammation (e.g., chronic HIV infection or Alzheimer's disease) in both humans and animal studies. However, whether the myo-inositol level measured with brain MRS reflects activation (i.e., increased numbers or cell volumes) of either astroglia or microglia or both is unknown. The current study correlated brain metabolites measured with MRS with two glial markers and a neuronal marker in cerebrospinal fluid (CSF), in a group of healthy participants and in chronically HIV-infected individuals.
Methods: We enrolled 42 healthy participants (age: 47.8 ± 2.1 years, 93% men) and 34 HIV subjects (age: 45.0 ± 1.6 years, 97% men) without other chronic medical or neuropsychiatric disorders, prior head injuries, confounding medication or history of severe drug use disorders. Each participant had a brain proton MRS (performed on a 3 Tesla MR scanner, TE/TR = 3000/30 ms, including correction for %CSF in the voxel) to measure brain metabolite concentrations the frontal white matter, and each had a lumbar puncture for CSF measurements of glial fibrillary acidic protein (GFAP) and Ionized calcium-Binding Adapter molecule 1 (Iba1), also known as Allograft Inflammatory Factor 1 (AIF-1), and neurofilament protein-light chain (NFL).
Results: All HIV subjects were stable on antiretroviral medications, had nadir CD4 count 181 ± 29/mm3 and Log viral load 2.6 ± 0.2 copies/mL (60% with undetectable viral load). More HIV subjects (38%) had HIV-associated neurocognitive disorder (HAND) than the controls (19% with HAND-equivalent). Compared to controls, HIV subjects had a trend for higher [AIF-1] ($p = 0.09$) but not for [GFAP] ($p = 0.21$) or NFL ($p = 0.18$), 1-way ANCOVA, covaried for age. Across both groups, an age-dependent increase was found in [AIF-1] ($r = 0.36$, $p = 0.0014$), but not for [GFAP] ($r = -0.01$, $p = 0.9$) or [NFL] ($r = 0.11$, $p = 0.34$) in the CSF. On MRS, frontal white matter myoinositol levels tended to be higher in HIV subjects than the controls ($+6.2\%$, $p = 0.09$) and showed greater age-dependent increases in HIV subjects than controls (ANCOVA-$p = 0.04$). Although the total choline compounds were not different between the two groups ($p = 0.42$), choline compounds also showed a steeper age-dependent increase in HIV subjects than controls (ANCOVA-$p = 0.002$). In multivariate analyses, myoinositol level correlated with age ($r = 0.35$, $p = 0.0001$) and with [AIF-1] ($r = 0.34$, $p = 0.004$), but not NFL or GFAP, across both groups. Also, the relationship between AIF-1 and [myoinositol] was independent of HIV status. Similarly, in the multivariate analyses, choline compounds tended to correlate with age ($r = 0.22$,

$p = 0.02$) and [AIF-1] ($r = 0.26$, $p = 0.02$) but not with [GFAP] ($r = 0.12$, $p = 0.33$) across both groups.
Conclusions: Consistent with prior reports, this group of clinically stable antiretroviral medication treated HIV patients has mild ongoing neuroinflammation, as shown by the mildly elevated myoinositol levels that becomes more evident with older age. Similar but less steep age-dependent increase in neuroinflammation is also observed in the healthy controls. Regardless of HIV status, however, myoinositol level, and to a lesser extent the level of choline compounds, measured with in vivo MRS in the brain correlated with the microglial marker [AIF-1] but not with astroglial marker [GFAP]. These findings suggest that elevated brain myoinositol levels measured on MRS in condition of chronic neuroinflammatoin primarily reflect microglial rather than astroglial activation, which is more prevalent in acute infections as seen in SIV studies. Furthermore, microglial activation appears to persist in our HIV subjects, especially in the older individuals, and to a lesser degree with normal aging. The level of myoinositol is a useful non-invasive biomaker to assess the degree of neuroinflammation in various neurodegenerative diseases and to monitor disease severity.
Keywords: myoinositol, microglia, astroglia, neuroinflammation.
Disclosure: Nothing to Disclose.

W117. Altered Expression of the Hyaluronan Receptor CD44 in Schizophrenia

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Background: Hyaluronan and chondroitin sulfate proteoglycans (CSPGs), are two major components of the extracellular matrix (ECM) in the brain, serving as the backbone and the organizers of the ECM, respectively. We recently reported pronounced alterations of CSPGs in the amygdala, entorhinal cortex, prefrontal cortex, and hippocampus of subjects with schizophrenia (SZ). In particular, we found altered numbers of glial cells and decreased number of perineuronal nets, ECM specialized aggregates enveloping distinct neuronal populations. As a step toward investigating potential mechanisms underlying the ECM abnormalities in SZ, we tested the involvement of CD44, a key hyaluronan receptor expressed on the cell surface of glial cells. CD44 is responsible for the organization of hyaluronan-based ECM, and has an important role during development and maturation of glial cells. CD44 is expressed by several types of glial cells in the adult human brain, including white matter astrocytes, perivascular glial cells, and glial cells unassociated with microvasculature. The central role of CD44 in regulation of the extracellular matrix turnover points to potential abnormalities of CD44 expression in subjects with SZ. The main goal of this study was to test the hypothesis that CD44 expression is decreased in subjects with SZ.
Methods: Paraformaldehyde fixed tissue blocks containing the amygdala from 12 control, 12 schizophrenic and 9 bipolar disorder subjects were obtained from Harvard Brain Tissue Resource Center. Stereology-based cell counts of CD44 immunoreactive glia in distinct amygdala nuclei was performed blindly to diagnostic group, using computer assisted quantitative light microscopy. CD44 immunoreactive cells were counted into two groups depending on their association, or lack thereof, with blood vessels. Step-wise regression analysis was used to test for statistical significance of changes relative to the main outcome values, taking into consideration potential confound variables such as age, gender, hemisphere, exposure to therapeutic and abuse drugs, and vascular pathology. To further investigate the phenotype of CD44 immunoreactive cells we used CD44 and glial fibrillary acidic protein (GFAP) dual immunofluorescence labeling and confocal microscopy analysis.
Results: Our results show that the numerical density of blood vessel-associated CD44 immunoreactive cells is significantly decreased in the basal ($p = 0.009$), accessory basal ($p = 0.02$), cortical ($p = 0.01$), medial ($p = 0.04$), and central ($p = 0.04$) nuclei of the amygdala. The numerical density of CD44 immunoreactive cells unassociated with blood vessels is decreased in basal ($p = 0.01$), accessory basal ($p = 0.02$) and medial ($p = 0.03$) nuclei. Numerical density of CD44 immunoreactive cells in subjects with bipolar disorder was only decreased in cells unassociated with blood vessels in the basal nucleus ($p = 0.01$). We found no effect of potentially confounding variables on the numerical density of CD44 immunoreactive glial cells. Majority of CD44 immunoreactive cells are GFAP positive.
Conclusions: The role of CD44 in regulating ECM properties, glia maturation, glia limitans layer of the blood brain barrier and interaction with immune cells, makes this molecule particularly relevant to the pathophysiology of SZ. To our knowledge, this is the first study to investigate CD44 abnormalities in this disorder. Our findings support the hypothesis that a dysregulation of CD44 expression in SZ may contribute to ECM pathology in this disorder. These results also add to emerging evidence for anomalous glia maturation in schizophrenia and suggest the possibility that the blood brain barrier may also be impacted, a possibility which will be investigated in future studies. Importantly, CD44 decrease may be specific to SZ, as the observed changes in bipolar disorder were relatively modest and other brain diseases such as stroke, multiple sclerosis, Alzheimer's disease, encephalitis, and seizures are all associated with increased CD44 expression.
Keywords: Schizophrenia, CD44, Amygdala, Postmortem.
Disclosure: Nothing to Disclose.

W118. Class II Metabotropic Glutamate Receptors Are Downregulated in Major Depressive Disorder

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Background: Major Depressive Disorder (MDD) affects ~10% of the world's population (WHO). Yet, despite high prevalence rates, major etiological questions remain un-

answered, and better therapeutic strategies are urgently needed. Emerging results aimed at identifying the mechanism of action of ketamine, an NMDA receptor antagonist that shows rapid and effective antidepressant activity, reveal a role for mGlu2/3 in the signaling pathways thought to underlie the antidepressant effects, necessitating further investigations into mGlu2 and 3, and their involvement in MDD. In this study, we investigated the expression of mGlu2/3 receptors in postmortem brain tissue of subjects with MDD.

Methods: [3H]LY341495 saturation binding curves were established in human cortical tissue. Autoradiography was carried out on sections incubated in 3nm [3H]LY341495, post-fixed, and apposed to plates for 3d prior to being imaged on a BAS system, and analyzed using AIS software. BA17 (visual cortex), BA24 (Anterior cingulate cortex), and BA46 (dorsolateral prefrontal cortex) were analyzed in MDD, schizophrenia (SCZ), bipolar (BPD) and controls (N = 14-15). To assess the potential confound of antidepressant effects on binding, rats were treated with fluoxetine, or imipramine for 28 days, and brains were collected and assessed as described above.

Results: Consistent with an important role for mGlu2/3 in MDD, [3H]LY341495 binding was significantly decreased in BA24 of MDD relative to control, but unchanged in the same region in SCZ and BPD. No significant changes were detected in BA17 or BA46. Antidepressant treatment did not impact [3H]LY341495 binding, in rat brain.

Conclusions: The emergence of ketamine as a treatment for depression has shifted the focus of affective research programs, underscoring the need for increased insight into glutamate's contribution to the etiology and treatment of psychiatric disease. We demonstrate dysregulation of mGlu2/3 in MDD, and begin to dissociate the roles of mGlu2 and mGlu3 in the action of ketamine. However dissociation of mGlu2 from mGlu3 is a critical next step, for precisely identifying the disruption. Understanding how these receptors are involved in psychopathology will allow for the development of more targeted treatment strategies.

Keywords: Depression, Glutamate, Postmortem.

Disclosure: Nothing to Disclose.

W119. Medial Frontal GABA is Lower in Older Schizophrenia and Related to Cognition and Functional Capacity

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Background: Gamma-butyric acid (GABA) dysfunction has been implicated in the pathophysiology of schizophrenia. Reduced expression of GAD67, a GABA synthesis enzyme, is a well-replicated molecular finding in schizophrenia. GABAergic interneurons are thought to facilitate the rhythmic entrainment of pyramidal cell discharge and their abnormalities may lead to cognitive dysfunctions in schizophrenia. Proton magnetic resonance spectroscopy (MRS) has enabled quantification of brain GABA concentrations in vivo but with traditional techniques about 50% of the GABA signal is contaminated with macromolecules. All studies of schizophrenia to date have used this method resulting in "GABA+". Several MRS studies of schizophrenia have reported abnormal but inconsistent findings, including increased (Ongur et al. 2010; Kegeles et al. 2012) or reduced GABA+ levels (Goto et al. 2010; Yoon et al. 2010; Kelemen et al. 2013; Rowland et al. 2013) in schizophrenia, depending upon antipsychotic and concomitant medication status, illness duration, and brain region. This study tested the hypothesis that older participants with schizophrenia would have lower medial frontal GABA levels compared to older control participants. We predicted that there would be no significant difference between younger participants with schizophrenia and controls. The relationships between GABA and psychiatric symptoms severity, processing speed and working memory, and functional capacity were examined. This is the largest MRS study of GABA in schizophrenia and the first to examine macromolecule suppressed GABA.

Methods: A total of one-hundred and forty-five participants completed this study but 7 were excluded due to poor data quality, leaving a total of 29 younger and 31 older in the schizophrenia group and 38 younger and 40 older in the control group. MR scanning was conducted on a 3T Siemens Tim Trio equipped with a 32-channel head coil. For detection of GABA, spectra were acquired from a medial frontal region that included the anterior cingulate (Brodmann areas 24 and 32) using a macromolecule-suppressed MEGA-Point REsolved Spectroscopy Sequence (MEGA-PRESS) sequence: TR/TE = 2000/68 ms, 14 ms editing pulses applied at 1.9 (ON) and 1.5 (OFF) ppm, and 256 averages; water unsuppressed 16 averages. Quantification was conducted with GANNET 2.0 toolkit, a Matlab program specifically developed for analysis of GABA MEGA-PRESS spectra Patients were evaluated for psychopathology with the Brief Psychiatric Rating Scale (BPRS) and the Brief Negative Symptom Scale (BNSS). Participants completed neuropsychological tests of processing speed with the digit symbol coding test and working memory with the digit sequencing test. Functional capacity was assessed with the UPSA.

Results: Results of age group X diagnostic group ANOVA with gender and smoking as covariates revealed a significant main diagnosis by age interaction ($F(1,132) = 5.9$, $p = 0.017$) indicating that GABA levels declined from younger to older groups in schizophrenia but less so in the control sample. Results of analysis of simple effects supported our a priori hypothesis that GABA levels were significantly lower in the older participants with schizophrenia compared to older controls ($t(66) = 3.1$, $p = 0.003$) but not between the younger control and schizophrenia groups ($t(67) = 0.25$, $p = 0.994$). Linear regression analyses revealed that age strongly predicted GABA levels in the schizophrenia group ($B = -0.6$, $t(59) = -6.42$, $p < 0.001$, $R2 = 0.42$) accounting for 42% of variance, but the effect of age was less in the control group ($B = -0.24$, $t(75) = -2.1$, $p = 0.036$, $R2 = 0.057$) accounting for 5.7% of the variance. GABA levels were not related to positive or negative symptom severity. Higher GABA was associated with better processing speed performance ($r = 0.22$, $p = 0.015$), func-

tional capacity ($r = 0.28$, $p = 0.002$), and working memory ($r = 0.33$, $p < 0.001$) in the combined sample. Further evaluation revealed that the magnitude of these relationships was stronger in the schizophrenia (r range 0.21-0.33) compared to the control (r range 0.06 – 0.23) group.
Conclusions: This is the first study to investigate in vivo medial frontal GABA levels in schizophrenia using MEGA-PRESS with macromolecule suppression. This is also the largest study of GABA levels in schizophrenia measured with MRS to date. These data suggest that GABA levels more rapidly decline with advancing age in the schizophrenia compared to the control group, and that developing interventions targeted at increasing GABA levels may improve functional outcomes and quality of life in older schizophrenia, a subset that is poorly understood yet presents a large cost burden to the health care system.
Keywords: schizophrenia, MRS, GABA, cognition.
Disclosure: Nothing to Disclose.

W120. Cannabis and Dopamine Synthesis Capacity: [18F]-DOPA Pet Studies of Cannabis and Tobacco Users

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Background: Cannabis is one of the most widely used recreational drugs in the world and it is often consumed with tobacco. Cannabis users are at elevated risk of mental disorders including psychosis and there is some evidence that cannabis users are at increased risk of adverse educational and occupational outcomes via a reduction in motivation i.e. causes apathy. The mesolimbic dopaminergic system mediates the processing of incentive stimuli, which in turn is modulated by endocannabinoid signalling. Both substance dependence and schizophrenia have been associated with abnormal striatal dopamine synthesis capacity. It had been proposed, although never directly tested, that the links between cannabis use, schizophrenia and apathy are mediated by altered dopamine synthesis capacity, which would increase psychosis risk by creating a state of aberrant salience.
Methods: We used [18F]-DOPA positron emission tomography (PET) to compare dopamine synthesis capacity in 19 young adult regular cannabis users who experienced cannabis-induced psychotic-like symptoms with 19 nonuser sex- and age-matched control subjects. In order to investigate the effects of moderate tobacco use on dopamine synthesis capacity, we also compared 15 cigarette smokers to 15 non-smoker matched controls. We investigated the relationship between dopamine synthesis capacity and apathy in 14 cannabis users. Lastly, we measured salience processing in 17 cannabis users compared to 17 controls using the Salience Attribution Task which provides behavioural measures of adaptive and aberrant salience processing.
Results: Compared to controls, cannabis users had reduced striatal dopamine synthesis capacity (effect size: .85; $t36 = 2.54$, $p = .016$) whilst moderate cigarette users did not ($t28 = .64$, $p = .53$). The group difference in dopamine synthesis capacity in cannabis users, compared with controls, was driven by users meeting diagnostic criteria for cannabis abuse or dependence. Dopamine synthesis capacity was negatively associated with higher levels of cannabis use ($r = -.77$, $p < .001$) and positively associated with age of onset of cannabis use ($r = .51$, $p = .027$), but was not associated with cannabis-induced psychotic-like symptoms. Levels of cigarette use were not related to striatal dopamine synthesis capacity. Cannabis users scored highly on self-rated apathy. Within cannabis users, striatal dopamine synthesis capacity was inversely correlated with subjective apathy ($rho = -.64$, $p = .015$). There were no differences in behavioural measures of salience processing between cannabis users and controls. Within Cannabis users there was a significant effect of dependency/abuse diagnosis on implicit aberrant salience ($F1,15 = 5.8$, $p = .03$) and a significant relationship between cannabis-induced psychotic-like symptom severity and explicit aberrant salience ($r = .61$, $p = .04$). In an exploratory analysis, compared to controls, cannabis users exhibit a loss of relationship between implicit salience processing and striatal dopamine synthesis capacity ($z = 2.12$, $p = .03$).
Conclusions: These findings indicate that long-term heavy cannabis use is associated with a dose-dependent reduction in striatal dopamine synthesis capacity. These results also indicate that our finding may be driven by cannabis users who meet diangnostic criteria for abuse or dependence. Reduced striatal dopamine synthesis capacity may underlie the reductions in reward sensitiy and amotivation associated with heavy long-term cannabis use. Since moderate cigarette smoking is not associated with altered striatal dopamine synthesis capacity, these findings are unlikely due to tobacco. These findings question the hypothesis that cannabis increases the risk of psychotic disorders by inducing the same dopaminergic alterations seen in schizophrenia. However, our findings of significant relationships between salience processing and cannabis-induced psychotic-like symptom severity, taken with preliminary evidence that dopaminergic mechanisms of salience processing are indeed altered with cannabis use suggest this hypothesis may require modification.
Keywords: Cannabis, Tobacco, Dopamine, PET.
Disclosure: Nothing to Disclose.

W121. Cerebrospinal Fluid Biomarkers in Iraq and Afghanistan Veterans: Effects of Deployment and Blast Concussion Mild Traumatic Brain Injury

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Background: Mild traumatic brain injury (mTBI) caused by exposure to improvised explosive devices has been termed the signature injury of the wars in Iraq and Afghanistan. Repetitive blast-induced mTBI, which is common among Iraq and Afghanistan service members and Veterans, may also pose a risk for neurodegenerative dementias such as

chronic traumatic encephalopathy, seen with increasing frequency among professional athletes with repetitive impact mTBIs. Objective biomarkers of mTBI would be useful for diagnosis, prognosis, and monitoring of response to potential treatments, as well as identifying mechanisms of neuronal injury and neurodegeneration.
Methods: Participants were 28 Iraq and/or Afghanistan Veterans with blast concussion mTBI, 13 deployed control Veterans, and 33 community controls. Deployed and community controls had no lifetime history of TBI. All subjects underwent careful clinical and neurocognitive assessment. CSF was collected between 0900-1100 hours following overnight fast using Sprotte 24g atraumatic spinal needles; CSF was aliquoted and frozen immediately at the bedside, and stored at -80deg C until assayed. CSF total tau, ptau181, Aß42, and a panel of cytokines were measured by multiplex bead-based Luminex assays (Innogenetics and Bio-Rad). Differences among participant groups were assessed using the Kruskal-Wallis test followed by pair-wise Wilcoxon tests with Bonferroni correction.
Results: mTBI Veterans had experienced an average of 14 blast exposures with acute symptoms consistent with VA/Dept. of Defense criteria for mTBI; last blast exposure was an average of 4 years prior to study participation. Interleukin (IL)-7 was elevated in mTBI Veterans compared to either deployed controls or community controls 15.7 ± 14.5, 8.46 ± 11.4, and 8.26 ± 7.98 pg/ml, respectively) demonstrating an effect of blast exposure ($p < 0.001$). IL-6 showed an effect of both deployment and additionally blast-induced mTBI (mTBI $= 3.42 \pm 2.86$, deployed controls $= 2.95 \pm 1.91$, and community controls $= 1.76 \pm 1.15$ pg/ml; $p < 0.05$). Eotaxin and granulocyte colony stimulating factor were elevated in both Veteran groups, with and without mTBI. Absolute values of CSF total tau, ptau181, Aß42 did not differ among groups; however, the ratio of ptau181 to total tau was elevated approximately 20% in both mTBI Veterans and deployed controls compared to community controls ($p < 0.001$).
Conclusions: These results provide CSF biomarker evidence of neurodegeneration and neuroimmune-related responses in Iraq and Afghanistan Veterans with both effects of mTBI and effects of deployment alone with or without mTBI. These CSF biomarker results are in keeping with our previous data showing similar blast mTBI-and separate deployment effects on structural and functional neuroimaging measures. Additional research is needed to elucidate specific pathogenic mechanisms attributable to blast exposure and those that may be the result of environmental exposure in the Iraq/Afghanistan combat theater.
Keywords: CSF, biomarker, veterans, concussion.
Disclosure: Nothing to Disclose.

W122. Changes in Serotonin Affect Raphé Functional Connectivity in Depression

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Background: Depression remains a great societal burden and a major treatment challenge. Most antidepressant medications target serotonergic raphé nuclei. Acute tryptophan depletion (ATD) modulates serotonin function. ATD-induced changes in raphé activity can be detected with functional MRI. Prior work suggests that these changes in raphé activity may occur in specific frequency ranges. To better understand the raphé's role in mood networks, we studied raphé functional connectivity in depression.
Methods: Fifteen depressed patients were treated with sertraline for twelve weeks and then scanned during ATD and sham conditions. For each subject in each condition, we used CONN toolbox to analyze resting state MRI functional connectivity between raphé and seeds from nine other depression-related regions (ROIs), including the bilateral thalamus, ventromedial and dorsolateral prefrontal cortices, and anterior and posterior cingulate cortices. A standard fMRI frequency filter (0.01 to 0.1 Hz) was applied to minimize physiologic artifact. Separate analyses were also conducted using narrower frequency bandpass filters. In second-level analyses, we computed the difference in functional connectivity between sham and ATD conditions for each raphé-to-ROI pair. We used a general linear model with separate categorical predictors for remitters and non-remitters, where remission was defined as post-sertraline treatment HAM-D score less than eight.
Results: Raphé-to-ROI functional connectivity of the full frequency band 0.01-0.1 Hz across all subjects revealed no significant ATD-induced changes. ATD decreased raphé functional connectivity with the bilateral thalamus within 0.025-0.05 Hz, and also decreased raphé functional connectivity with the right pregenual anterior cingulate cortex within 0.05-0.1 Hz. Post-hoc analysis by remission status suggested increased raphé functional connectivity with left pregenual anterior cingulate cortex in remitters ($n = 10$) and decreased raphé functional connectivity with left thalamus in non-remitters ($n = 5$), both within 0.025-0.05 Hz.
Conclusions: This study replicates prior findings for raphé-thalamus functional connectivity changes at specific frequencies in an independent sample. To our knowledge this is the first report of ATD effects on raphé functional connectivity in prospectively-treated depression. There are several possible physiologic explanations for the observed ATD-induced functional connectivity changes. One possibility is that these relationships represent slow oscillators and that ATD-induced functional connectivity changes are a proxy for serotonergic effects on physiologically-important slow oscillations. This variability may relate to feedback mechanisms within the serotonin system, but this warrants further study. Among many limitations of this study, small sample size limits interpretation. Future studies of depression should examine clinical implications of alterations in raphé functional connectivity. For examination of serotonergic modulation of mood-related networks by functional MRI, specifying narrower frequency bands may enhance detection of regions implicated in neural circuitry and enable physiologically-relevant interpretation of functional connectivity measures.
Keywords: Raphé, Thalamus, fMRI Functional Connectivity, Serotonin.
Disclosure: Nothing to Disclose.

W123. Plasticity of the Dopaminergic System in Fear Conditioning and Extinction

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Background: A conditioned dopamine (DA) response has been found to occur during associative learning with reward in humans. In animal studies, DA has also been shown to play a role in associative learning with aversive cues, also known as fear conditioning. A 'fear circuit' implicated in fear conditioning studies with animals includes the amygdala, hippocampus, nucleus accumbens, ventral tegmental area-substantia nigra, and the medial prefrontal cortex (mPFC); in addition, the extinction of fear learning has been shown to involve the ventromedial prefrontal cortex. Although activity in these areas has been reported in humans during fear conditioning, little is known about the dopaminergic correlates/activity. The current study uses PET and 18F-Fallypride to investigate DA release in nodes of the fear circuit, in healthy adults, during fear conditioning and extinction.
Methods: Five healthy volunteers have completed the study to date. All showed an adequate acute physiological response to the aversive stimulus, a mild electric shock to the wrist (heart rate increase of >1SD, or skin conductance response increase of $>10\%$). PET imaging was carried out using a high-resolution research tomograph (HRRT) and 18F-Fallypride to measure DA release in brain regions of interest (ROI). After an initial PET scan without shock exposure, participants learned to associate the electric shock with a neutral cue through a trace conditioning procedure with a 30% contingency rate. Participants were then presented with the shock-paired stimulus during a second PET scan. Lastly, the association between the conditioned stimulus and aversive shock was extinguished by repeatedly presenting the cue in the absence of the electric shock, and participants then had a third and final PET scan while being repeatedly exposed to the extinguished cue. ROI analyses were performed on binding potential (BP) data. The skin conductance response (SCR), heart rate (HR) and plasma cortisol levels were measured as physiological measures of fear throughout all sessions. Subjective ratings were also recorded to assess whether the correct association was learned, and to measure the level of anxiety experienced by participants in response to the neutral cues.
Results: Following the fear conditioning regimen, the shock-paired cue significantly increased SCR ($p<0.05$) and lowered BP in the mPFC (18% displacement of 18F-Fallypride, $p=0.047$), as compared to baseline. Following extinction, the SCR fear response was significantly reduced ($p<0.05$) and BP was lower than baseline in the posterior cingulate gyrus (PCG; 18% displacement; $p<0.01$). The significant decreases in BP in these regions suggest increases in DA release as compared to baseline. No other significant differences in BP between scans were observed in other nodes of the fear circuit ($p>0.05$).
Conclusions: These very preliminary findings suggest that DA release in the mPFC plays a role in the expression of fear conditioning. Interestingly, the PCG, a region believed to be involved in the default mode network, appears to be, in this initial sample, an important region for dopaminergic control of extinction. Advancing our understanding of the specific neurochemical mechanisms underlying fear learning and extinction may have implications for the pathophysiology and treatment of stress and anxiety related disorders.
Keywords: PET, Dopamine, Fear conditioning, Extinction.
Disclosure: Nothing to Disclose.

W124. Cerebral Bioenergetics and Membrane Phospholipid Metabolites in Schizophrenia and Familial At-risk State

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Background: Altered cerebral bioenergetics and membrane phospholipid (MPL) metabolites are repeatedly noted in schizophrenia (SZ). However, their association with at-risk states are not systematically investigated. Altered MPL metabolites have been reported in both SZ and those at risk from very few selected brain regions. A variety of morphometric and functional brain changes are reported among both SZ and HR by several groups including us. In vivo biochemical changes underlying these changes are less well understood. MPL metabolites include MPL precursors [phosphocholine (PC) and phosphoethanolamine (PE)] and catabolites [glycerophosphocholine (GPC) and glycerophosphoethanolamine (GPE)]. Elevated PE in early postnatal development that linearly decreases through adolescence and elevated PC at the time and site of neuropil growth spurts suggests relative specificity of the MPL precursor level changes to increases demand for MPLs in different neurodevelopmental and adaptational contexts. Likewise, the pruning of excessive synapses reflecting maturation leads to increased GPC and GPE. Animal studies and human postmortem studies show that less than 10% of the MPL metabolite changes are contributed by glial and neuronal somal changes. Adenosine triphosphate (ATP) is an essential source of energy for most biochemical reactions in the neurons. Conversion of adenosine diphosphate (ADP) to ATP is tightly coupled to phosphocreatine (PCr) that anaerobically donate high energy phosphate (HEP) moiety to ADP to form ATP in the first 2-7 seconds of intense neuronal activity. During low and sustained activity, PCr levels are normalized or may be elevated. We examined both MPL metabolites and HEP among early course SZ, HR and HC comprehensively across the brain in 21 anatomically precisely defined voxels.
Methods: We acquired whole-brain, multi-voxel 3D phosphorus CSI magnetic resonance spectroscopy (31P MRS) data at 3 Tesla on 92 subjects (SZ = 36, HR = 22, HC = 34). Mean ages of SZ subjects (24.36 ± 6.94 years) did not differ from HR subjects (22.96 ± 3.73 years) but HR subjects were significantly younger than HC (26.97 ± 7.52 years; $p=0.02$). The voxels of interest (VOI) included 21 grey matter voxels (e.g. the prefrontal cortex (PFC), hippocampus, caudate, thalamus). Post-processing was done by shifting the 3D CSI

voxel grid relative to the anatomical images prior to the Fourier Transform in order to extract and quantitate the 31P signal within the VOI, which was fully automated. The metabolite quantification (PE, PC, GPC, GPE, PCr, ATP, dinucleotides and inorganic orthophosphate) of the extracted 31P signal of each voxel was 100% automated and metabolite levels were expressed as a mole % of the total signal. We used Generalized Linear Models to examine group differences using age, sex and grey matter proportion within the voxel as covariates (SAS PROC GENMOD).

Results: MPL metabolites: Main effect of diagnosis was noted in the dorsal hippocampus for PE + PC ($p = 0.03$) with no differences in GPE + GPC. SZ subjects and HR showed increased PE + PC compared to controls with no difference between the SZ and HR. Ventral hippocampus showed a trend for the diagnosis effect ($p = 0.057$) with an increase in PC + PE among SZ compared to HC. Posthoc within diagnostic groups tests (SZ vs HR; HR vs HC; SZ vs HC) showed increased GPE + GPC in the PFC ($p = 0.042$), calcarine cortex ($p = 0.012$), ventral occipital cortex ($p = 0.037$), and increased PE + PC in the PFC (0.039) and ventral hippocampus (0.039) among SZ compared to HC. HR showed increased GPE + GPC in the superior parietal lobule ($p = 0.024$), and increased PE + PC in the dorsal hippocampus ($p = 0.023$) compared to HC. Energy metabolites: Main effect of diagnosis on ATP and PCr was observed in the caudate and ventral occipital cortex. ATP was decreased and PCr was increased in both SZ and HR compared to HC in both regions with no significant difference between HR and SZ. Posthoc within diagnostic group differences showed increased ATP in the thalamus ($p = 0.04$) and the dorsal hippocampus ($p = 0.039$) with no changes in PCr among SZ compared to HC.

Conclusions: MPL metabolite and bioenergetic changes are observed in distinctly different brain regions among SZ and HR compared to HC. PC + PE elevation suggest an increased synapse formation and density in the PFC and hippocampus among both SZ and HR compared to controls with no significant differences between SZ and HR. The latter may suggest that the dorsal hippocampal neuropil density among HR may be similar to that of SZ and could serve as a marker of risk for SZ. The HEP changes (elevated PCr and decreased ATP) in the caudate and occipital regions but not in the hippocampus and PFC suggest reduced resting state caudate neuronal activity. Functional imaging data suggest decreased working memory task-related connectivity between the caudate and PFC in SZ. Decreased intrinsic neuronal energy metabolism may partly explain such poor connectivity between the caudate and PFC. Taken together, these data suggest that SZ and HR subjects show similar patterns of dual impairments in neuropil density and decreased neuronal energy metabolism. Longitudinal studies using MPL turnover rates as a predictor could identify individuals at higher risk for future conversion to psychosis.

Keywords: Neuropil, Bioenergetics, Schizophrenia, Neurodevelopment.

Disclosure: Nothing to Disclose.

W125. The Brain State Induced by Physical Activity: Effects on Cortical Glutamate, GABA and Neuroplasticity in Humans

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Background: Physical activity evokes a marked elevation in non-oxidative brain metabolism (suggesting increased de novo neurotransmitter synthesis) and an excitatory shift in the balance of cortical excitation and inhibition (suggesting enhanced neuroplasticity). These changes have been described as a distinct "brain state" induced by physical activity and are modulated by noradrenergic and cholinergic circuits. These exercise-induced changes appear to oppose those observed in the brain state characterizing major depressive disorder (MDD) and may mediate some of the antidepressant effects of exercise. In primary visual cortex (V1), recent studies have shown that exercise induces both an excitatory shift in the cortical excitation-inhibition balance measured with cellular imaging and an increase in cortical glutamate level measured with 1H-MRS. The current studies had four goals: 1) to examine whether exercise-induced increases in glutamate are confined to sensory and motor regions or are also observed in prefrontal regions showing low glutamate in MDD (anterior cingulate cortex (ACC)); 2) to test whether exercise evokes an increase in only glutamate or an increase in both glutamate and GABA in V1; 3) to examine the possibility that T2 relaxation changes influence the effects of exercise on MRS-visible glutamate; and 4) to test whether exercise acutely increases neuroplasticity in V1 and hippocampus as evidenced by enhanced learning of behavioral tasks mediated by these regions.

Methods: Thirty healthy young adults participated in a series of single voxel, 3-Tesla, 1H-MRS studies of the acute effects of exercise on glutamate (PRESS, $N = 16$) and GABA (MEGA-PRESS, $N = 6$) in V1, and on glutamate in ACC (PRESS, $N = 8$). In 8 additional subjects, short echo time (TE) (30 ms) and intermediate TE (144 ms) PRESS spectra were acquired from V1 in a interleaved fashion to examine the possible influence of T2 relaxation changes on the observed exercise-induced effects. LCModel was used to quantify metabolite values from PRESS acquisitions, and custom software was used to quantify GABA from MEGA-PRESS acquisitions. A second group of healthy young adults participated in cognitive studies examining acute exercise-induced changes in neuroplasticity mediated by the hippocampus (relational memory, $N = 29$) and by V1 (visual perceptual learning, $N = 27$).

Results: 1H-MRS PRESS spectra (TE/TR = 144/1500) were acquired from V1 and ACC immediately before and from 16 to 40 minutes after 20 minutes of cycle ergometer exercise (mean peak heart rate = 94% of predicted max, mean peak Watts = 184). We observed a significant increase in glutamate after exercise in both V1 (5.2%, $p = .03$, effect size $d = 0.76$) and ACC (5.2%, $p = .002$, $d = 1.49$). Glutamate values were highest during the first post exercise measurement (acquired 16-24 minutes post exercise). Neither glutamine nor any other metabolites changed after exercise.

A similar experiment in a smaller sample using MEGA-PRESS (TE/TR = 68/1500) showed a significant increase in both GABA (7.7%, p = .02, d = 1.15) and glutamate (6.6%, p = .03, d = 0.99) in V1. A third study showed that the glutamate increase in V1 with exercise was similar whether measured using short (30ms) or intermediate (144 ms) TE (6.9%, p = .03, d = 0.76, and 5.5%, p = .03 d = 0.79, respectively). Additional subjects performed cognitive tests beginning 5 minutes after either a 20-minute epoch of vigorous exercise or a 20-minute rest period during counterbalanced testing sessions approximately one week apart. The Relational and Item Specific Encoding task (RISE) was used to test hippocampally-relational memory. Relational memory performance was significantly better after exercise than after rest (p = .02, d = 0.40). Perceptual learning of a contrast discrimination task was used to assess visual cortical plasticity. We observed non-significantly greater visual perceptual learning after exercise than after rest (p = .085, effect size = 0.26).

Conclusions: The results support the hypothesis that the brain state induced by exercise includes a widespread increase in the synthesis of glutamate and possibly GABA. MDD is characterized by reduced glutamate in the ACC, as well as other prefrontal regions and hippocampus. Many effective antidepressant treatments increase hippocampal and cortical neuroplasticity in animals. The current results suggest that the brain state induced by vigorous exercise may oppose the glutamate abnormality associated with MDD as well as enhance hippocampal neuroplasticity in humans. V1 neuroplasticity may be similarly enhanced by exercise. It is likely that the clinical potential of physical activity in treating MDD has not yet been fully realized. Uncertainty about optimal activity regimens and about which patients are most likely to benefit currently limits the utility of exercise interventions. MRS and cognitive measures may have value as intermediate outcome variables in studies comparing different exercise regimens. Assessing the acute effects of exercise on these measures in individual patients may help identify the patients most likely to benefit from an exercise intervention.

Keywords: glutamate, GABA, exercise, depression.
Disclosure: Nothing to Disclose.

W126. Similar Abnormalities in Modular Network Organization in Anorexia Nervosa and Body Dysmorphic Disorder

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Background: Anorexia nervosa (AN) and body dysmorphic disorder (BDD) are frequently co-occurring psychiatric disorders, both involving distortions of body image, obsessional thought and compulsive behaviors, and poor insight. However, to date there have been no published studies comparing their neurobiological features. To understand similarities and differences in brain connectivity in AN and BDD, we analyzed whole-brain white matter networks using graph theory analyses. Graph theory provides quantitative measurements of complex brain networks, to provide information about organizational systems as a whole. In graph theory, complex networks may consist of a number of modules, each containing several interconnected nodes. Modularity is a statistic that quantifies the degree to which the network may be subdivided into such clearly delineated modules. Previous studies in several psychiatric populations have found abnormal patterns of network modularity, although this has never been tested in AN or BDD. We tested for abnormalities in modularity in AN and BDD compared with healthy controls. Further, we tested for relationships between regional network metrics within the modules and symptom severity in each disorder.

Methods: Participants: Participants included 86 unmedicated individuals, aged 13 to 38 years, in three groups: BDD (n = 31), weight-restored AN (n = 24), and healthy controls (n = 31) of equivalent age and sex. MRI data acquisition: We acquired data using a Siemens 3T scanner. Diffusion-weighted MRI was acquired along 64 gradient directions with b = 1000s/mm2 and one minimally diffusion-weighted scan. High-resolution T1-weighted images were acquired with an MPRAGE sequence. Network construction: We computed whole-brain deterministic DTI tractography, and conducted cortical and subcortical parcellation using Freesurfer to yield 87 regions of interest (ROIs). For each pair of ROIs we determined the fiber count connecting them, which then defines the corresponding entry in the DTI-based structural connectome. To extract the modular configuration of these connectomes, we used the standard modularity metric as well as the Path Length Associated Community Estimation technique (PLACE), an in-house developed method for reconstructing hierarchical modularity of a brain connectome using top-down bifurcating trees. Using the healthy control group as a reference group, we tested for group modular differences using two-sample Hotelling T-squared test, Bonferroni corrected for multiple comparisons. For the nodes found to have abnormal modular patterns relative to controls, we calculated Pearson's correlation coefficients between symptom severity, anxiety, and degree of insight with nodal path length (the principal determinant of modular affiliations under PLACE) and a scalar metric V that quantifies nodal modular abnormality (V ranges from 0 to 1; 0 indicates no modular pattern is shared at this node while 1 indicates a complete match).

Results: There were no significant group differences using the standard modularity metric. For PLACE, the AN group showed significant abnormalities in one module (P < .01, corrected); while the healthy control group showed a modular affiliation among the right caudate, pallidum, nucleus accumbens, caudal and rostral anterior cingulate, and posterior cingulate, in the AN group the corresponding module included the right lateral and medial orbitofrontal cortices and the frontal pole, but not the pallidum, caudal anterior cingulate, or posterior cingulate. In the BDD group, there was a trend for similar frontostriatal abnormalities in the same module (P < .051, corrected); in the BDD group this module also included the medial orbitofrontal cortex, but did not include the nucleus accumbens or caudal anterior cingulate. Correlation analyses with clinical vari-

ables demonstrated that in the AN group, poor insight correlates with longer path length in the right caudal anterior cingulate ($r = .51$, $P = .044$) and the right posterior cingulate ($r = .53$, $P = .035$).
Conclusions: Results demonstrate abnormal network community organization in individuals with AN. Specifically, a right frontostriatal module includes orbitofrontal cortex in AN, but not in healthy controls; a similar pattern is demonstrated in the BDD group. This suggests shared abnormalities in frontostriatal network organization in AN and BDD. In addition, in two gray matter regions within this module lower efficiency of information transfer was associated with worse insight in AN. The inclusion in this module of nodes that are commonly implicated in obsessive-compulsive disorder (OCD) (anterior cingulate, orbitofrontal cortex, and caudate), combined with shared phenomenology of obsessive thoughts and compulsive behaviors, suggest possible overlapping aberrant white matter neurocircuitry underpinning OCD-related pathophysiology in BDD and AN. Future studies that compare network organization directly to individuals with OCD are warranted to further elucidate this relationship.
Keywords: anorexia nervosa, body dysmorphic disorder, connectome, graph theory.
Disclosure: Nothing to Disclose.

W127. Regulation of Neural Responses to Emotion by Ketamine in Individuals with Treatment-resistant Major Depression

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Background: The glutamate N-methyl-d-aspartate (NMDA) receptor antagonist ketamine has demonstrated antidepressant effects in individuals with treatment-resistant major depressive disorder (TRD) within 24 hours of a single dose. The current study utilized functional magnetic resonance imaging (fMRI) and two emotion perception tasks involving happy, sad and neutral facial expressions in order to examine the neural effects of ketamine in patients with TRD.
Methods: Twenty patients with TRD free of concomitant antidepressant medication underwent fMRI at baseline and 24 hours following administration of a single intravenous dose of ketamine (0.5 mg/kg). Adequate data was available for 18 patients for each task. Twenty age- and sex-matched healthy volunteers were scanned at one time point for baseline comparison. Whole-brain, voxelwise neuroimaging analyses were conducted controlling for a family-wise error rate (FWE) of $p < 0.05$.
Results: Compared to healthy volunteers, TRD patients showed reduced neural responses to positive faces within the right caudate. Following ketamine, neural responses to positive faces were selectively increased within a similar region of right caudate. Connectivity analyses showed that greater connectivity of the right caudate during positive emotion perception was associated with improvement in depression severity following ketamine. No main effects of group or time were observed for the sad faces task.
Conclusions: Our results indicate that ketamine specifically enhances neural responses to positive emotion within the caudate in depressed individuals in a pattern that appears to reverse baseline deficits. Clinical improvement following ketamine is associated with connectivity of the caudate during positive emotion processing.
Keywords: depression, antidepressant, ketamine, imaging.
Disclosure: In the past 2 years, Dr. Murrough has served on advisory boards for Janssen Research and Development and Genentech and has provided consultation services for ProPhase, LLC and Impel Neuropharma. Dr. Iosifescu has received funding (through Icahn School of Medicine at Mount Sinai) from AstraZeneca, Brainsway, Euthymics, Neosync, Roche and Shire; and consulting fees from Avanir, CNS Response, Lundbeck, Otsuka, Servier and Sunovion. Dr. Dennis Charney (Dean of Icahn School of Medicine at Mount Sinai), and Icahn School of Medicine at Mount Sinai have been named on a use patent on ketamine for the treatment of depression. The Icahn School of Medicine has entered into a licensing agreement for the use of ketamine as therapy for treatment-resistant depression. Dr. Charney and Icahn School of Medicine at Mount Sinai could potentially benefit if ketamine were to gain approve for the treatment of depression. In the past 12 months, Dr. Mathew has received consulting fees from Bristol-Myers Squibb, Genentech, and Naurex, and research support from AstraZeneca and Janssen Research and Development. All other authors report no conflicts of interest.

W128. Metadoxine Reduced Brain Activity in Neural Circuits Associated with Cognitive Dysfunctions: A Pharmacological MRI Study in Conscious Rats

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Background: Metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate) is an ion-pair salt of pyridoxine (Vitamin B6) and pyrrolidone carboxylate (PCA). A phase IIb placebo-controlled clinical trial has demonstrated the efficacy of Metadoxine Extended Release (MDX) in adults with ADHD. We have previously reported that metadoxine works through antagonism of the serotonergic 5-HT2B receptor and increased inhibitory gamma-aminobutyric acid (GABA)-ergic synaptic transmission via a pre-synaptic effect in the cortico-striatal network. In order to further elucidate and fingerprint the region-specific brain activity of metadoxine, brain responses to a single administration of metadoxine were investigated using the pharmacological magnetic resonance imaging (phMRI) in awake rats, a non-invasive tool based on the blood oxygen level-dependent (BOLD) effect, yielding functional activation brain mapping with high temporal and spatial resolution.
Methods: 36 adult male Sprague-Dawley rats were subjected to phMRI. All animals were acclimated to the restrainer device and imaging system once daily for 5 days before imaging to reduce a stress-induced response. Following the

acclimation period, animals were slightly anesthetized with 3% isoflurane, placed in the restrainer and positioned in the magnet. When fully conscious, rats were administered a single intraperitoneal injection of vehicle (water for injection), 75 or 150 mg/kg metadoxine and then subjected to imaging using a Bruker Biospec 7.0T/20-cm USR horizontal magnet (Bruker, Billerica, Massachusetts) and a 20-G/cm magnetic field gradient insert capable of a 120-μs rise time (Bruker). Functional images were acquired continuously every 6 seconds repeated 600 times for a 60-minute scan (5 minute baseline; 55 minutes post-injection). Anatomical images were collected and registered to a 3-D segmented rat brain atlas (Ekam Imaging). Statistical analyses were performed on imaging data using a non-parametric Kruskal-Wallis multiple comparison test comparing the average signal intensity in each voxel for their 5 minutes baseline scan to activity at 45-50 minutes post-dose.

Results: Metadoxine exhibited a significant dose-dependent decreased brain activity when examined at 45-55 min post administration, as indicated by widespread negative BOLD activity in 28 brain regions out of 170 regions evaluated. The main areas displaying a significant ($p < 0.05$) reduction in the volume of activation (i.e increased negative BOLD) include the prefrontal cortex (PFC) (including prelimbic, 2nd motor, medial orbital, anterior cingulate), thalamic nuclei, dorsal striatum (caudate putamen) and multiple subregions of the cerebellum. Primary somatosensory areas were significantly suppressed by metadoxine as well. Only 7 areas out of 170 showed a significant increased positive BOLD response, two of them being the central nucleus of the amygdala and the lateral hypothalamus, while the lateral orbital cortex exhibited significant dose-dependent decrease in positive BOLD. The central nucleus of the amygdala plays a key role in mediating fear- and anxiety-related behavioral responses. The amygdala is interconnected with subcortical regions (orbitofrontal (OFC) and anterior cingulate cortex. The OFC and the amygdala communicate via a negative feedback loop and this bidirectional communication provides a potential basis for the integration of cognitive, attention, working memory, emotional, and physiological processes. None of the mesolimbic dopamine system brain regions (ventral tegmental area, substantia nigra, nucleus accumbens, ventral pallidum, bed nucleus of stria terminalis) known to be involved in the reinforcing effects of scheduled drugs were significantly affected by metadoxine.

Conclusions: Metadoxine produces a specific and extensive effect of reduced brain activity as indicated by widespread negative BOLD in brain areas related to executive function, motivation, information processing, attention and cognition. The PFC, caudate putamen, thalamus and cerebellum are interconnected, having anatomical and functional interactions. These neuronal circuits have been reported to be dysregulated in cognitive dysfunctions, and altered activity of these brain regions is thought to contribute to the pathophysiology of ADHD. Metadoxine displays a distinct phMRI fingerprint as compared with approved ADHD therapies, the main difference being fewer areas exhibiting positive BOLD and a lack of effect on abuse-related brain regions. These results suggest that metadoxine may restore cortical, striatal and cerebellar hyperactivation by reducing neuronal activity in these affected systems, which could explain the pro-cognitive activity of metadoxine in ADHD. These findings further confirm and extend our previous data demonstrating a novel monoamine-independent mechanism of action of metadoxine characterized by GABAergic inhibitory transmission modulation.

Keywords: phMRI, Metadoxine, ADHD, BOLD.

Disclosure: Johanna Schumann, Jonathan Rubin and Yaron Daniely are full-time employees and own stock or stock options in Alcobra Inc or Alcobra Ltd. Craig Ferris is a full-time employee of Northeastern University, has a financial interest and has completed research that was funded by Alcobra Ltd. Mark Nedelman is the president and full-time employee of Ekam Imaging, has a financial interest in the company and has completed research that was funded by Alcobra Ltd.

W129. Gene Expression Profiles of ECT Response in Major Depressive Disorder

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Background: A major contributor to the disease burden of Major Depressive Disorder (MDD) is the typically lengthy period between the initiation of treatment and clinical improvement. Antidepressant medications usually require many weeks to months before most individuals experience an amelioration of symptoms, and many patients require trials of two or more different agents before obtaining demonstrable clinical benefit. Electroconvulsive therapy (ECT), a well-established treatment which often yields full remission of symptoms within 2-4 weeks, is typically utilized only with patients who have failed to respond to standard therapies. However, ECT is particularly valuable as a fast-acting treatment intervention to elucidate the pathways underlying rapid response and treatment failure. Peripheral blood gene expression profiles provide useful surrogates of brain-mediated changes following such fast-acting interventions. Based on evidence that processes underlying neurogenesis and neuroplasticity are altered in MDD, and that increased neurogenesis may be critical for an antidepressant response, we examined gene expression profiles in MDD patients undergoing ECT.

Methods: The data presented here are part of a larger NIMH-funded project designed to investigate multimodal correlates of ECT response in MDD. Patients with recurrent MDD in a major depressive episode who were referred to receive ECT as part of their routine care were recruited to take part in four research sessions, which were scheduled within 48 hours before the 1st ECT treatment (T0), less than 24 hours after the 2nd ECT treatment (T1), within one week (T2) and 6 months (T3) after completion of the ECT index series. A demographically matched sample of healthy controls completed two testing sessions, which were scheduled approximately 1 month apart (to match T0 and T2 for patients). The majority of patients received right unilateral ECT using the seizure threshold titration method; all participants were tapered off antidepressant pharma-

cotherapy prior to initiation of ECT. Clinical response to ECT was assessed primarily with the MADRS. To assay levels of genetic activity at each time point, total mRNA from peripheral blood was amplified, labeled and hybridized on Illumina Expression RefSeq HT-12 BeadArrays, which queries genome-wide gene expression. Following a standard preprocessing pipeline, we conducted analyses to isolate changes in gene expression associated with an effect of ECT (ECT-Related gene set), and effect of MDD (Disease-Related gene set). Subsequently, we conducted network analyses (Weighted Gene Co-Expression Network Analysis, WGCNA) to identify groups of highly co-expressed genes (modules) and identify key gene networks associated with treatment response.

Results: Analyses presented here are based on blood samples collected from a sample of 25 MDD patients (25, 22, and 14 of which have completed T2, T3, and T4, respectively), and 22 controls. There was a significant reduction in depressive symptoms at post-ECT index series from baseline, with 64% of the patients meeting criteria for response ($\geq$ 50% change in MADRS scores). We identified robust changes in gene expression as a result of ECT, and between MDD patients and controls, with observed expression differences significantly greater than expected by chance. Furthermore, there was a significant overlap in ECT-Related and Disease-Related gene sets, with evidence for a reversal of Disease-Related expression patterns following ECT in MDD patients. After reducing the dimensionality of data with network analyses, we identified an ECT-Related and a Disease-Related module of co-expressed genes, after correcting for multiple comparisons. Interrogation of gene networks revealed an enrichment of brain-enriched genes, with key genes involved in synaptic plasticity. Specifically, our results identified top ECT-Related genes that are known to play a specific role in hippocampal neurogenesis.

Conclusions: Our results demonstrate that an effect of ECT is detectable in peripheral blood expression samples in a group of patients with recurrent MDD. These results fill a gap in our understanding of the mechanisms underlying response to fast-acting treatment interventions. While there is evidence to suggest increase hippocampal neurogenesis in animal models of ECT, and evidence in human samples to suggest changes in brain structure and function (especially the hippocampus) underlying treatment response to ECT, there has of yet been no evidence regarding genomic changes underlying a fast-acting treatment response in humans. We suggest that our results reflect a genomic signal of neuroplastic processes underlying treatment response, which provide support for the neurotrophic hypothesis of antidepressant action in MDD. Replicating our findings in an independent sample, and in patients receiving alternative fast-acting treatment interventions, is necessary. This line of research has the potential to uncover biomarkers that help identify individuals at risk for MDD or for relapse, and may guide the use of alternate or more aggressive individualized treatment strategies.

Keywords: Biomarker, Genomic, ECT, Neuroplasticity.
Disclosure: Nothing to Disclose.

W130. The Differential Effects of an Index Course of Magnetic Seizure Therapy and Electroconvulsive Therapy on Autobiographical Memory Specificity

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Background: Magnetic seizure therapy (MST) uses magnetic pulses to induce a focal seizure for the treatment of depression. This strategy capitalizes upon the established safety of transcranial magnetic stimulation and the robust antidepressant efficacy of seizures as induced with electroconvulsive therapy (ECT). A recognized cognitive side effect of ECT is retrograde amnesia for autobiographical information. Preclinical and clinical evidence has substantiated that MST produces little to no neurocognitive adverse effects. However, no studies have compared the effects of ECT and MST on autobiographical recall, and importantly on autobiographical memory specificity. The specificity of autobiographical recall is a critical cognitive function that has been found to be a cognitive marker of depression, as well as a predictive factor for depressive relapse. Thus, the purpose of this study was to compare the effects of an index course of high-dose MST and right unilateral ultrabrief pulse width ECT on autobiographical memory recall and specificity in patients with a current major depressive episode.

Methods: This was a three-center, between-subject, randomized, double-masked controlled clinical trial that compared the neurocognitive effects of high dose MST and ultra-brief pulse RUL ECT. All participants provided written informed consent for this IRB approved investigation before completing study procedures. The study was conducted under a US FDA IDE. Adults with a major depressive episode in the context of unipolar or bipolar depression, based on the SCID-I, were randomly assigned to treatment with MST or ECT. For MST, a Magstim Theta device with a round coil positioned on the vertex was used to administer the stimulus. Seizure threshold was titrated at the first session by increasing the train duration, and subsequent treatments were provided at maximal device output (100% maximal pulse amplitude, 100 Hz pulse frequency, 10 second train duration). For ECT, treatments were provided via standard RUL electrode configuration, 800 mA or 900mA pulse amplitude, and ultra-brief pulse width (0.3 ms). Seizure threshold was titrated at the first session by increasing the train duration and frequency. Subsequent treatments were provided at $6\times$ the seizure threshold. Patients were treated until they achieved remission (<8 on the 24-item Hamilton Rating Scale for Depression) or received a maximum of 14 MST or ECT sessions. To assess autobiographical memory and autobiographical memory specificity, we used the Autobiographical Memory Test (AMT). Trained neuropsychometricians, masked to treatment condition, administered the AMT before and after the acute course. The AMT produced three variables including total memories recalled, total categoric memories, and total specific memories. ANOVAs were computed for each AMT variable with treatment condition (MST, ECT) as the

between-subject factor. We explored effects of covariates including study site, number of treatments, and change in depression severity. However, the covariates had no effects and were excluded from the statistical analyse.
Results: In terms of change from baseline to end, patients who received MST relative to those who received ECT showed better recall of autobiographical memories ($F(1,35) = 4.61$, $p = 0.04$), and better autobiographical memory specificity ($F(1,35) = 6.25$, $p = 0.02$). Indeed, the patients in the ECT group showed a 25% decline in autobiographical recall and a 25% decline in autobiographical memory specificity. However, the patients in the MST group showed no change in recall of autobiographical memories and approximately 15% improvement in autobiographical memory specificity.
Conclusions: This is the first study to provide evidence that MST has neurocognitive advantages relative to ECT, particularly with regard to recall of autobiographical information and autobiographical memory specificity. If the latter is indeed a cognitive marker of depression, then this could provide useful information regarding underlying mechanisms of the high relapse rate associated with ECT and provide an avenue to understand the antidepressant durability of MST. These findings are consistent with prior research suggesting MST to have no neurocognitive adverse effects, or cognitive enhancing effects. Research has found that autobiographical recall worsens after acute treatment with ECT, which is associated with select ECT parameters including bitemporal electrode placement, sine wave pulse width, and increased dosage. Future research is warranted to determine the underlying mechanisms of the neurocognitive improvement observed with MST, and to examine its effects on other cognitive domains.
Keywords: Magnetic seizure therapy, electroconvulsive therapy, depression, neuropsychology.
Disclosure: Research support from the Stanley Medical Research Institute; equipment donated by Magstim, Ltd.

W131. Post-mortem Volumetric Analysis of Nucleus Accumbens in Heroin Addiction: Implications for Deep Brain Stimulation

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Background: Deep brain stimulation (DBS), especially stimulation of the Nucleus accumbens (NAc), is increasingly investigated in neuropsychiatric disorders such as addiction. In addiction, NAc plays a central role as one of the key nuclei of the brain reward system, which is highly affected by and becomes dysfunctional through psychotropic substances. DBS requires computer-assisted 3D planning to implant the stimulation electrode precisely at the intended target in the brain. However, planning of target coordinates also relies on data from stereotactic atlases (such as the Schaltenbrand-Atlas) which has been collected and then standardized from only few healthy individuals. Recently, there has been a debate in the scientific literature about the true dimensions of NAc in healthy as well as mentally ill individuals. Knowing its true dimensions in different neuropsychiatric disorders may improve even more precise targeting of NAc for therapeutic DBS.
Methods: Volumes of NAc of heroin addicted individuals ($n = 12$) and matched controls ($n = 12$) from the Magdeburg Brain Bank were calculated by using morphometry of serial whole-brain sections. As the addicted individuals were quite young at time of death (mean 31.8 ± 7.8), it was not possible, to completely match controls by age (mean 44.4 ± 10.5). Histologic and planimetric procedures were performed, as previously described by us in detail (Bielau et al. 2005; Baumann et al. 1999): Every 25th serial coronal whole brain section (thickness 20 μm) was stained with a combined Nissl-Myelin (Heidenain-Wölcke o/luxol fast blue) staining, resulting in an intersectional distance of 0.5 mm. Measurements of cross-sectional areas of the structures were performed by planimetry from 4-fold magnifications of the sections. Structure volumes were calculated by multiplying cross sectional areas by the distance between the sections and adding up volumes obtained by this procedure along the entire rostro-caudal axis of the NAc. Estimated NAc volume in the heroin group was calculated using the ratio of NAc volume to total brain volume of the control group and total brain volume of the heroin group.
Results: Total brain volume was larger in the heroin group compared to controls (mean 1487.5 ± 62.9 cm3 vs. mean 1352.4 ± 103.2 cm3) as the heroin group was younger by over 10 years. Interestingly, despite younger age, total volumes of NAc were lower in the heroin group (left NAc 252.2 ± 62.7 mm3; right NAc 239.3 ± 91.8 mm3) compared to controls (left NAc 295.7 ± 91.2 mm3; right NAc 283.7 ± 94.6 mm3). Comparing the ratios of volume of NAc to total brain volume, the difference of the left NAc was statistically significant ($p = 0.030$). NAc volumes in the heroin group are reduced by 22.4% (23.3% for the right NAc) compared to the estimated volume.
Conclusions: To our knowledge, this is the first study to investigate NAc volumes in heroin addiction. Given the estimated volume reduction by over 20%, we believe it is important to further analyze NAc volumes (and 3D shapes) in different psychiatric disorders. Knowing its true dimensions will help to improve precise targeting and electrode placement even further. Our study did not focus on the reasons of the volume reduction. While specific toxic effects of heroin on NAc seem possible, addiction could also be the consequence of a possible predisposition to addiction due to early developmental abnormality of NAc.
Keywords: Nucleus accumbens, Heroine, Addiction, Deep Brain Stimulation.
Disclosure: Nothing to Disclose.

W132. Preliminary Efficacy of 5 Hz Repetitive Transcranial Magnetic Stimulation for Depression and Comorbid Anxiety

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Background: Repetitive transcranial magnetic stimulation (rTMS) is a safe and effective treatment for major

depressive disorder (MDD). While stimulation pulsed at a frequency of 10 Hz dominates clinical treatment protocols to date, a number of rTMS treatment parameters (e.g., treatment intensity, frequency, and total pulses delivered) can be manipulated to enhance efficacy or tolerability. Previous studies have utilized 5 Hz rTMS for depressed patients. Based on those clinical results, and in light of electroencephalogram (EEG) data demonstrating association of altered theta band signals (i.e., 4-7 Hz) with depressive and anxiety states, we investigated the relative efficacy of rTMS delivered at 5 Hz versus 10 Hz to the left dorsolateral prefrontal cortex (DLPFC) for MDD patients in a naturalistic setting.

Methods: A retrospective chart review was performed on adult outpatients who received clinical rTMS at Butler Hospital, Providence, RI, between 2009 and 2014. Inclusion criteria were broad in order to best represent the clinical rTMS treatment population: 1) a primary diagnosis of MDD, 2) completion of an acute course of 15 or more rTMS treatments to the left DLPFC, 3) naïve to rTMS therapy prior to the index acute course of rTMS therapy, and 4) completion of standardized symptom assessments at pre-rTMS baseline and at one or more time points after starting rTMS treatments. rTMS was delivered as an adjunct to the ongoing psychotropic medication regimen. Two stimulation protocols were used for treatment: 10Hz (i.e., 4-second stimulation train, 26-second inter-train interval) or 5 Hz (4-second stimulation train, 12-second inter-train interval). All patients started on the 10 Hz protocol, and change to 5 Hz rTMS was implemented according to clinical judgment as needed at any point during the treatment series based on the emergence of insomnia, anxiety, or psychomotor agitation. The sample was split into two groups based on the treatment frequency at which $>50\%$ of total pulses were delivered. Comorbid anxiety was defined by regular daily use of anxiolytic medications at the start of the treatment series. Baseline and endpoint depressive symptoms were assessed using standard clinical rating scales for depression (the 9-Item Patient Health Questionnaire [PHQ-9] and Inventory of Depressive Symptoms-Self Report [IDS-SR]).

Results: Ninety-eight patients met inclusion criteria for this analysis. Mean $\pm$ SD age for the sample was 51 ± 12.8 years, with 72% female; age and gender did not differ between the 5 Hz ($n = 27$) and 10 Hz ($n = 71$) groups. Baseline IDS-SR scores were significantly higher in the 5 Hz group (51.6 ± 8) than in the 10 Hz group (46.8 ± 9.6; $p = .024$), but baseline PHQ-9 scores did not differ significantly (18.8 ± 5 vs. 19.2 ± 4, $p = .785$). Patients receiving 5 Hz were more likely to have comorbid anxiety (85%), compared with patients in the 10 Hz group (51%)($\chi 2 = 9.7$, $p = .002$). There was a statistical trend for greater exposure to antidepressant medications in the current episode in the 5 Hz group (6.6 ± 4.6 vs. 4.9 ± 4 medications in the 5 Hz and 10 Hz groups, respectively, $p = .069$. The total number of treatment sessions was 35.4 ± 7.2 and did not differ between groups ($p = .545$). The 5 Hz group received an average of 24 treatments at 5 Hz, and the 10 Hz group received an average of three 5 Hz treatments. Similar efficacy outcomes were observed in both groups, as reflected by lack of statistically significant difference on post-treatment IDS-SR scores (28.8 ± 14.2 and 25.3 ± 14.9, for 5 and 10 Hz groups, respectively; $p = .283$) and PHQ-9 scores (8.8 ± 7 vs. 9.2 ± 5, $p = .833$). Remission and response rates on the IDS-SR did not significantly differ (all $p > .1$) between groups: 28.6% and 53.1%, respectively, using IDS-SR criteria, and 28.9% and 60.2% respectively, using PHQ-9 criteria.

Conclusions: Naturalistic treatment results from our clinic suggest that antidepressant outcomes following rTMS delivered at 5 Hz are similar to those achieved with the standard "on-label" 10 Hz protocol. This finding is notable in light of the fact that those who got 5 Hz had more severe depression at baseline and were more likely to have comorbid anxiety. These data indicate the need for prospective studies evaluating the efficacy of 5 Hz rTMS in patients with MDD and comorbid anxiety.

Keywords: repetitive transcranial magnetic stimulation, depression, anxiety.

Disclosure: Drs. Noah Philip, Audrey Tyrka, Lawrence Price and Linda Carpenter have received research support from Neuronetics Inc., NeoSync Inc., and Cervel Neurotech Inc., through clinical trial contracts. Ms. Carpenter and Mr. Sanchez have no disclosures.

W133. Increased Cognitive Flexibility as a Potential Mechanism of Ventral Capsule/Ventral Striatum Deep Brain Stimulation: A Combined Behavior/EEG Pilot Study

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Background: Deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS) is an effective treatment for obsessive-compulsive disorder (OCD), with ongoing research in major depressive disorder (MDD). Little is understood about the mechanisms of VC/VS DBS, despite hypotheses of effects on learning, motivation, and cognition. As a result, we have limited ability to pre-select patients who are likely to benefit from this invasive and expensive treatment. Moreover, once a stimulator is implanted, we are not readily able to titrate therapy to treat a biological or neurological marker. This limits our ability to effectively set stimulation parameters.

Methods: We studied ten VC/VS responders diagnosed with MDD and/or OCD. Subjects completed the Multiple Source Interference Task (MSIT) with DBS ON, then again after an hour with DBS OFF. In the intervening time, subjects' brain activity presumably relaxed towards the pathologic state. This has been documented in animals using similar paradigms (Ewing & Grace 2013), but this is the first study of the same effect in humans. We recorded 60-channel EEG during task performance, then analyzed behavior and event-related potentials (ERP) in sensor space. Comparisons within and across subjects were implemented with non-parametric randomizations, using cluster-based threshold correction across neighboring sensors.

Results: Correct decision-making was faster with DBS ON (32.5ms, $F = 21.3$, $p < 0.0001$). In a companion experiment

recorded on the same day under the same conditions, subjects were required to press a button rapidly to earn rewards. There was no significant difference in pressing speed in the ON vs. OFF condition, ruling out psychomotor effects. The enhancement of decision-making speed was stronger under cognitive interference (267.5 vs. 250.8ms, $p < 0.0003$, Tukey HSD). ERP showed a weaker negative potential at rostral midline electrodes during interference with DBS ON ($p = 0.02$, Bonferroni corrected), centered at 100-150ms after stimulus onset. This is consistent with the N200, whose magnitude classically reflects cognitive conflict and reflects an increased demand on neural resources caused by conflicting/ambiguous stimuli.

Conclusions: VC/VS DBS improved processing of cognitive interference stimuli, reflected in both decision times and neural activation. The significant change in ERP is in anterior midline electrodes, generally considered to reflect potentials arising in the anterior cingulate cortex. This structure is often described as a "conflict detector" that slows neural computations globally in order to accurately converge the processing of ambiguous stimuli. Our results are consistent with a hypothesis that VC/VS ameliorates MDD/OCD by improving patients' ability to process ambiguous or conflicting information. Clinically, this may correlate with the anecdotal observation that patients are better able to utilize cognitive-behavioral therapy skills after VC/VS stimulation.

Keywords: neuromodulation, brain stimulation, DBS, EEG.

Disclosure: Nothing to Disclose.

W134. Transcranial Direct Current Stimulation (tDCS) in Obsessive-Compulsive Disorder: A Review of Emerging Clinical Evidence and Considerations for Optimal Electrodes Montage

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Background: Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder with a 2% lifetime prevalence. Over the last decades, with the greater understanding of the brain circuits involved in OCD, non-pharmacological techniques for the treatment of this disorder have expanded. Such techniques include repetitive transcranial magnetic stimulation (rTMS) and deep brain stimulation (DBS) in targeted brain areas. However, the mixed findings regarding rTMS and the invasive characteristic of DBS highlight the need for the improvement and development of novel techniques. In this context, transcranial direct current stimulation (tDCS), a safe and relatively low cost neuromodulation technique that has been succesfully used in the treatment for major depressive disorder, might also be a potential new treatment for OCD, although the optimal tDCS montage remains unclear. This study aims to perform a systematic review on meta-analyses and pooled-analyses of DBS and rTMS trials for OCD and, based on these findings, to identify brain stimulation targets for the development of a double-blind, placebo-controlled, randomized tDCS trial. We also aimed to support the empirical evidence with computer head modeling analysis for the prediction of current flow between tDCS electrodes.

Methods: This is a qualitative review of the meta-analyses and pooled-analyses studies summarizing the findings of the rTMS and DBS trials for OCD published between January 2004 and May 2014 and searched in the MEDLINE, Scopus and Cochrane Library databases. Inclusion criteria: the studies should contain quantitative analysis of rTMS or DBS trials for OCD. For the tDCS computational analysis, we employed individualized models incorporating segmentation of cortical and subcortical structures of interest.

Results: Out of 146 references, only 3 matched our eligibility criteria: two DBS reviews (one meta-analysis and one pooled-analysis) and one rTMS meta-analysis. The most promising results regarding rTMS intervention were the low frequency stimulation in the supplementary motor area (SMA) and in the orbito-frontal cortex (OFC). Although DBS stimulation studies in general reported greater treatment response rates than rTMS, in most of the DBS studies factors such as the lack of standardization in the intervention parameters and the small sample sizes created difficulties in the comparison between the efficacy of different brain targets. Most of the studies performed DBS in the ventral striatum and the ventral capsule (VS/VC). Based on these findings and in the nature of tDCS intervention, we simulated possible montages to neuromodulate the following targeted areas: inferior VS, superior VS, ventral putamen, supplementary motor area and OFC. We found that the different targets can produce significant changes in the current direction and activation of specific brain areas. More specifically, we found that the inferior ventral striatum model seems to activate a greater number of structures related to OCD, in particular, the pre-frontal cortex and the anterior basal ganglia.

Conclusions: There is evidence that hyper-activation of the obitofronto-thalamic circuits and lack of inhibition of the cortico-striato-thalamo-cortical (CSTC) pathways are implicated in OCD pathophysiology. CSTC circuits convey information flow from cortical and limbic regions to modulate motivation, attention, and motor function. The key structures of these circuits include the dorsolateral prefrontal cortex, the orbitofrontal cortex, the anterior cingulate cortex, and the striatum (specifically the caudate). The supplementary motor area has been also of interest due to its extensive connections with regions implicated in cognition and motor control. Considering that the aim of a tDCS trial for OCD would be to perform an inhibitory stimulation in pre-frontal and subcortical structures such as the anterior basal ganglia, computer models developed for this study suggested that the most promising model for the objectives of the trial would be targeting the inferior ventral striatum. This model seems to stimulate the largest number of structures of interest with considerable specificity.

Keywords: obsessive-compulsive disorder, neuromodulation, transcranial direct current stimulation.

Disclosure: Dr. Marom Bikson is the inventor of technologies dealing with transcranial electrical stimulation for which The City College of New York holds patents.

W135. Response of Depression to Electroconvulsive Therapy: A Meta-Analysis of Clinical Predictors

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Background: Patients with severe, refractory depression have few treatment options. Electroconvulsive therapy (ECT) remains the most effective treatment available. But ECT is also burdensome, and roughly one-third of individuals with depression do not respond. Reliable clinical or biological predictors of ECT response would be clinically useful but have not been demonstrated definitively. We used meta-analysis to measure effect sizes for a series of clinical predictors of ECT response in depression.
Methods: PubMed was searched systematically to identify studies published after 1980 that tested at least one clinical predictor of response to ECT. The weighted mean odds ratio (OR) or standardized mean difference (SMD) was computed for each of 10 clinical predictors, based on dichotomous outcomes (responder versus non-responder). Statistical analyses examined robustness, bias, and heterogeneity.
Results: We identified 32 articles, examining 10 clinical predictors, that were compatible with meta-analysis. Shorter episode duration predicted higher ECT response rate (SMD = -0.37, 7 studies, 702 subjects, $P = 0.000004$). History of medication failure in the current episode was also a robust predictor: response rates were 58% and 70%, respectively, for those with and without medication failure (OR = 0.56, 11 studies, 1175 subjects, $P = 0.00001$). Greater age and psychotic features were weakly associated with higher ECT response rates, but heterogeneity across studies was notable. Bipolar diagnosis, sex, age at onset, and number of previous episodes were not significant predictors. Analyses of symptom severity and melancholic features were inconclusive due to study heterogeneity.
Conclusions: Longer depressive episodes and medication failure are robust predictors of poor response to ECT. Effect sizes for these two predictors are modest but clinically relevant. Surprisingly, commonly assessed characteristics like age, psychotic features, and melancholic features are not as robust, and are less likely to be clinically useful. Discovery of other clinical and biological predictors would be useful for stratifying patients who have severe, refractory depression. Clinically useful biomarkers of ECT response must provide additional predictive power beyond that of episode duration and medication failure.
Keywords: depression, electroconvulsive therapy, predictors, treatment resistance.
Disclosure: Nothing to Disclose.

W136. Preliminary Investigation of an Emotion Regulation Circuitry-targeted Psychological Intervention for Mood Disorders in Adolescents and Young Adults

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Background: Adolescence/young adulthood is a period of dynamic development of brain systems that subserve emotion regulation and that have repeatedly been shown to be involved in Bipolar Disorder (BD). The majority of individuals with BD also transition from sub-threshold symptoms to fully-syndromal disorder during this period. This suggests that adolescence/young adulthood may be a critical period in the development of BD, when interventions that improve emotion self-regulation and normalize activity in emotional brain circuitry may peak in their beneficial effects on neurodevelopmental and behavioral trajectories and, therefore, illness course and prognosis. This pilot study examined the effect of a new psychological treatment, the Emotion Self-Monitoring and Regulation Therapy (E-SMART), on a target brain system central in emotional regulation, including the ventral prefrontal cortex (VPFC) and its major connection site, the amygdala, as well as associated emotional regulation and mood symptoms. The E-SMART consists of twelve one-to-one meetings (including in-person and video teleconferencing) and between session assignments. The intervention builds on concepts of emotional regulation, self-control, and regulation of daily routines. It is designed to develop specific skills to improve self-regulation over responses to emotional stimuli, while promoting regularity of daily sleep and activity routines to promote mood stabilization.
Methods: Seven adolescents and young adults participated in comprehensive diagnostic, symptom and behavioral assessment, E-SMART and reassessment after the intervention. A subset of subjects participated in functional magnetic resonance imaging (fMRI) scanning, during processing of emotional face stimuli, before and after the treatment. Changes in emotional regulation [Difficulties in Emotion Regulation Scale (DERS)], depressive symptoms [Hamilton Rating Scale for Depression (HRDS)], manic symptoms [Young Mania Rating Scale (YMRS), Clinician Administered Rating Scale for Mania (CARS-M)], fMRI activation and functional connectivity were investigated. Associations between neural circuitry and symptom changes were also evaluated.
Results: E-SMART was associated with significant decreases in difficulties in emotion regulation ($p < 0.05$) and depressive symptoms ($p < 0.05$). Neural circuitry changes from pre- to post-ESMART included reductions in amygdala responses ($p < 0.05$) and increases in VPFC responses ($p < 0.01$), to fearful face stimuli, as well as increases in amygdala to VPFC functional connectivity during fearful face processing ($p < 0.05$). Changes in neural circuitry functioning showed associations with symptom reductions, including $r = -0.53$ for manic symptoms and VPFC activation and $r = -0.98$ for depressive symptoms and VPFC functional connectivity.
Conclusions: This pilot study provides preliminary evidence that E-SMART is associated with decreases in emotional regulation difficulties and improvements in mood symptoms, and emotional regulation circuitry changes. The observed association between the symptom changes and brain changes suggests that the intervention may lead to enhanced mood stability through improving the ability of the VPFC to provide adaptive inhibitory control over responses in the amygdala, suggesting further study of this treatment is warranted. This new intervention for BD shows considerable promise as a circuitry-targeted psychological treatment, with potential to contribute to under-

standing of brain mechanisms underlying emotional dysregulation, BD and their treatment.
Keywords: Mood Disorders, Adolescent, Psychotherapy, Magnetic Resonance Imaging.
Disclosure: Nothing to Disclose.

W137. Evaluating the Effectiveness of Contingency Management on One Month of Cannabis Abstinence in Cannabis Dependent Individuals with and without Schizophrenia

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Background: Cannabis use disorders (CUD) are highly prevalent in patients with schizophrenia compared to the general population and are known to adversely affect the course of the disorder insofar as clinical symptoms, functional outcomes and deleterious effects on cognition. Despite the high rates of this addiction, there are no approved pharmacological interventions for treating CUDs, and therefore novel interventions should be considered. Data examining contingency management (CM) among cannabis-dependent patients with schizophrenia is limited. This study evaluated the effectiveness of employing a CM intervention to maintain one-month of cannabis abstinence in non-treatment seeking cannabis dependent patients with schizophrenia versus cannabis dependent non-psychiatric controls.
Methods: Thirteen schizophrenia patients with cannabis dependence and 13 cannabis dependent non-psychiatric controls underwent one-month of cannabis abstinence supported by a CM intervention. Baseline and weekly visits included assessments of clinical symptoms including craving and withdrawal and cognition was assessed biweekly. Participants received weekly supportive therapy sessions in conjunction with CM, which began on Day 14. Participants who provided cannabis-free urine samples were rewarded with the chance to win a prize. On Day 28 if abstinence was biochemically established, participants were entitled to a $300 bonus. Twice weekly urine analysis was used to confirm abstinence, which later was tested by gas chromatography-mass spectrometry to obtain quantitative cannabis metabolite levels (11-nor-9-carboxyl-THC).
Results: To date, 25/26 participants who engaged in the cannabis abstinence program have completed the study. Of completers, 9/12 (75%) schizophrenia patients and 9/13 (69%) non-psychiatric controls have achieved end-point urine toxicology-verified THC abstinence. Associations between clinical and cognitive symptoms in the schizophrenia and control groups and abstinence rates will also be presented.
Conclusions: Preliminary results are promising and demonstrate the feasibility and effectiveness of implementing a CM intervention in both a cannabis dependent psychiatric and control population. Future research should investigate CM in treatment seeking individuals and using longer abstinence periods.
Keywords: schizophrenia, cannabis, contingency management.
Disclosure: Dr. George has received consulting fees from Novartis and investigator-initiated research funding from Pfizer.

W138. Functional Connectivity Focal Electrically Administered Seizure Therapy (FEAST) Using High Resolution EEG

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Background: Electroconvulsive therapy (ECT) efficacy and cognitive side effects remain influenced by several parameters including electrodes position and configuration, the applied current intensity, duration, and polarity. We propose the use of a nonlinear interaction model in multichannel scalp EEG recordings paired with ECT and determine the functional interaction across cortical areas.
Methods: Patients were treated with FEAST using a modified MECTA spECTrum 5000Q device (MECTA Corp, Tualatin, Oregon) and following the same anesthesia protocol. Titration and 2 treatment sessions at 6 times seizure threshold (6*ST) involved a simultaneous 64 channel EEG recording (Neuroscan, Compumedics). We derived the non-linear dynamic interaction models from modified neuronal population activity models whose dynamics can reproduce basic features of ECT-induced seizures within local areas and across distant cortical areas. We applied the Square-Root Cubature Kalman filter in three EEG states: baseline under general anesthesia, ictal and post-ictal. This yielded the functional connectivity between right and left frontal and parietal regions. In addition, we computed the global power relative to baseline for ictal and post-ictal phases.
Results: To date, we acquired 22 recordings from 8 patients with major depressive disorder (4 females, age $= 44.5 \pm 10$ years). These included 6 titration sessions (28.7 ± 10 mC), 8 6*ST direct polarity and 8 6*ST reversed polarity (172.8 ± 59.48 mC). Frontal and parietal ictal parameters showed a significant difference in functional connectivity values (4.07 ± 2.98, -0.46 ± 0.34, $p < 0.001$). Right frontal region also showed a significant difference in relative ictal power changes from baseline between titration and treatment sessions (-0.16 ± 0.07, -0.26 ± 0.09, $p = 0.037$). No differences were found in the post-ictal phase (0.24 ± 0.14, 0.33 ± 0.14, $p = 0.25$) nor between direct and reversed polarity.
Conclusions: This innovative research highlights the regional relationships of ictal and post-ictal activity with FEAST. Although no changes were observed between direct and reversed polarity treatment administration, FEAST is clearly initiating seizure activity in the frontal region (right > left). Ongoing analyses are focusing on regional interactions and detailed power spectra. Future work will focus on comparing FEAST with more classic ECT modalities and relationship to clinical outcomes.
Keywords: ECT, FEAST, EEG, Seizure.
Disclosure: MECTA donated the devise for research. Curtis Ponton is an employee of Neuroscan.

W139. Preliminary Test of Amber Glasses as a Way of Resetting Circadian Melatonin Release: Randomized Trial During Travel from Asia

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Background: The neural and genetic circuitry controlling circadian rhythms is intimately bound to mood, energy, and cognitive functioning (Wirz-Justice, 2007; Zelinski et al., 2014). Transmeridian travel provides a challenge paradigm, disrupting the circadian system in otherwise healthy individuals (Brown et al., 2009; Sack, 2009). Experts have long recommended pre-adaptation, shifting periods of sleep and activity to the new schedule ahead of travel, as a method for reducing jet lag (Arendt, 2009; Coste & Lagarde, 2009). However, pre-adaptation is more difficult when traveling east, as it would require going to bed earlier, or when traveling between the Americas and Asia – requiring circadian reversal. Recent work established that non-image forming retinal cells connect to the suprachiasmatic nucleus and entrain the body's master clock and control the dim light melatonin onset (DLMO) (Thapan, Arendt, & Skene, 2001). The photoreceptor in these cells, melanopsin, has its peak sensitivity to short wavelengths of light in the blue and blue-green spectrum. Blocking these wavelengths triggers the DLMO in both animal and human studies (Burkhart & Phelps, 2009; Sasseville, Paquet, Sevigny, & Hebert, 2006). Amber glasses may provide a feasible way of blocking the target light spectra while allowing other wavelengths through. In theory, shifting the time one starts wearing the amber glasses could shift the DLMO, making it possible to pre-adjust for transmeridian travel. The primary objective was to evaluate the efficacy of amber glasses and a pre-adaptation schedule to reduce the sleep and mood effects of jet lag. Blue glasses provided a placebo condition, blocking a similar percentage of visible light, but outside the range affecting melanopsin in the intrinsically photosensitive retinal ganglion cells (ipRGCs). Hypotheses included that amber glasses would be associated with significantly less circadian disruption following travel from Asia to Europe or North America, less negative mood and more positive affect following travel, and more rapid restabilization of sleep.
Methods: Participants were 24 adults (age 35-70 years, 42% female) all teaching at an international summer campus at a university in Seoul, South Korea. This created a natural experiment where all participants were similar on a variety of variables that affect circadian rhythms, including: work schedule, living quarters, educational attainment, geographical location and seasonality, and socio-economic status. Participants were stratified based on age, gender, target time zone, and morningness-eveningness preference, and randomly assigned to either amber glasses or blue glasses. Additional faculty members were recruited to a "no glasses" matched control group, completing the same rating scales. All participants completed the Morningness-Eveningness Questionnaire at baseline, along with past week PANAS mood ratings and the Pittsburgh Sleep Quality Index (PSQI). Participants repeated the PANAS and PSQI weekly, up to three times prior to travel day, and twice upon arrival at their destination. They also completed a daily sleep diary that recorded zeitgebers as well as daily ratings of sleep quality and energy on a 0 (abysmal) to 5 (excellent) scale. Mixed regression models assessed the time*treatment interactions on mood, sleep quality, sleep problems, and energy ratings.
Results: The amber glasses were associated with large effects on sleep, measured via the PSQI as well as sleep diary. The blue glasses were not significantly different than the "no glasses" control, as anticipated based on the animal models and wavelengths of sensitivity for the ipRGC melanopsin receptors. Amber glasses were associated with less increase in negative affect following travel and phase shift with jet lag.
Conclusions: Results were consistent with a growing body of literature indicating that amber glasses block sufficient amounts of blue and blue-green light to trigger endogenous melatonin secretion (Burkhart & Phelps, 2009). Shifting the time of wearing glasses was able to move the timing of circadian rhythms, pre-adjusting for transmeridian travel and reducing the effects of jetlag. Findings support the possibility of using amber glasses as a form of "virtual dark" therapy, potentially helping regulate mood as well as sleep (Phelps, 2008). Limitations include the sample size, which precluded examining the effects of different adaptation schedules. Future work should include actimetry ratings and salivary melatonin assays, as well as test the limits of how rapidly it is possible to shift schedules. Moving two or three hours in a day would make the protocol more feasible, provided that the circadian cycle still adjusted.
Keywords: circadian rhythm, melatonin, sleep, jet lag.
Disclosure: Nothing to Disclose.

W140. Hippocampal Connectivity Changes Associated with Electroconvulsive Therapy Response

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Background: The increased volume and structural changes associated with ECT-induced plasticity within the hippocampus belie the otherwise paradoxical relationship between ECT and cognitive function. Despite the improvement in mood and depressive symptoms, ECT participants often report and show cognitive difficulties during the ECT series. ECT-induced cognitive impairment may be related to transient disruption in previously acquired enhanced synaptic transmission or long-term potentiation (LTP) (McClintock et al., 2014). In animal models, electrically induced seizures have been shown to disrupt LTP (Anwyl et al., 1987; Hesse and Teyler, 1976). The disruption in LTP also provides a useful framework for testing ECT-induced cognitive impairment with resting state fMRI, which has been shown to follow Hebbian-like rules with respect to increased and decreased temporal coherence (Harmelech et al., 2013). Thus, decreased hippocampal functional connectivity during or immediately after the ECT may be indicative of this transient disruption in LTP. Here, we assess the relationship between hippo-

campal resting state fMRI functional connectivity and neuropsychological performance among older, depressed subjects before and after an ECT series.
Methods: Depressed subjects met the following inclusion criteria: 1) DSM-IV TR diagnosis of MDD; 2) the clinical indications for ECT; and 3) a Hamilton Depression Rating Scale–24 item (HDRS–24) > 21. Cognitive function was assessed pre- and post-ECT with the Repeatable Assessment for Neuropsychological Status (RBANS) and the Trail Making Tests Parts A and B. Depressed subjects were on psychotropic medications, but medication changes were limited to dosage changes between the two imaging assessments. Depressed subjects were scanned before and after the ECT series. A Thymatron System IV delivered a right unilateral (n = 22) or bitemporal (n = 3) stimulus delivery. Seizure threshold obtained during the first session with a dose titration method guided subsequent stimulus dosage (6 x threshold for right unilateral, 2 x threshold for bitemporal). Treatments occurred thrice weekly until adequate clinical response or clinical decision to stop treatment for non-responders. Resting state fMRI data were preprocessed with SPM8 (realignment, spatial normalization smoothing 8mm kernel). Voxels with high temporal standard deviation (> 0.98) associated with non-neuronal, artifactual, nuisance? signals were used as regressors with tCompCor, a component based noise correction reduction? method (Behzadi 2007). The data was despiked with Analysis of Functional NeuroImages (AFNI) and then bandpass filtered (0.008 to 0.09 Hz). We created a study-specific hippocampal mask from the Freesurfer volumes, which were eroded by dropping voxels where less than 90% of the subjects contributed to the summed hippocampal mask. The region of interest (ROI) averaged time courses for the right and left hippocampal masks generated correlation maps that were then r-to-z transformed. We used a ROI to ROI analysis to assess changes in connectivity with regions that have direct hippocampal connections: orbital frontal cortex, anterior cingulate, amygdala, nucleus accumbens, and posterior cingulate. Change in depressive severity, number of ECT treatments, days post-ECT, and neuropsychological performance were used to predict changes in hippocampal connectivity.
Results: ECT participants (n = 25, 64 years + /-8, 8 males) received 11 + /2.4 treatments within the ECT series. The post-ECT HDRS-24 confirmed clinical response from a pre-ECT assessment of 33.8 + /- 8.1 to a post-ECT assessment of 9.4 + /- 10.4. The RBANS delayed memory (t = 5.7, P < 0.001), Trail Making Test Part B (t = 3.2, P = 0.01), number of ECT treatments (t = -4.8, P = 0.001), and number of days from series to post-ECT assessment (t = 3.23, P = 0.01) predicted changes in connectivity between the left hippocampus and the left posterior cingulate, which was unrelated to ECT response (t = -1.88, P = 0.10). The right hippocampal connectivity changes were not associated with neuropsychological performance (P > 0.10).
Conclusions: To our knowledge, this is the first longitudinal ECT investigation to assess both symptom response and neuropsychological performance with resting state fMRI. Consistent with our hypothesis, decreased connectivity between the left hippocampus and the left posterior cingulate proximal to the ECT series appears to be related to ECT-mediated cognitive impairment. This disruption is transient and unrelated to the clinical response but commonly results in frustration among patients and family members alike.
Keywords: major depressive disorder, electroconvulsive therapy, fMRI, neural plasticity.
Disclosure: Nothing to Disclose.

W141. Moodswings 2.0 (www.moodswings.net.au): An Online Intervention for Bipolar Disorder–Report from the Front

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Background: The application of adjunctive psychosocial interventions in bipolar disorder is often limited in the real world due to cost and access constraints. MoodSwings 1.0 was an Australian online self-help program for people with bipolar disorder adapted from a validated group-based face-to-face program. MoodSwings 1.0 compared the online delivery of MoodSwings Plus (interactive tools plus psychoeducation) with MoodSwings (psychoeducation alone), with both groups using the same platform and having access to small group moderated discussion boards. Participants diagnosed with bipolar I or II disorder (n = 156) were randomised and over 12 months, improvement in both groups showed baseline to endpoint reductions in mood symptoms and improvements in quality of life, functionality, and medication adherence. MoodSwings Plus was noted to be superior to MoodSwings in improvement on symptoms of mania at 12 months (p = 0.02). MoodSwings 2.0, an updated and enhanced program, was developed in response to these promising findings and is currently being evaluated internationally.
Methods: Participants diagnosed with bipolar I, II or NOS are actively being recruited. MoodSwings 2.0 is a 2-site, parallel group, stepped design where participants are randomized to one of three arms: (1) moderated peer discussion board only, 2) discussion board plus psychoeducation, or 3) discussion board, psychoeducation, and online interactive psychosocial tools. The study's two sites (Palo Alto, CA, and Melbourne, Australia) will enroll 300 participants globally – not limited to the USA and Australia. Outcomes will be assessed at quarterly intervals via phone interview with raters blind to group assignment as well as via online self-report.
Results: The primary outcomes of MoodSwings 2.0 will be changes in depressive and manic symptoms over 12 months, assessing if there is additive benefit to the three components (education, discussion board, and interactive psychosocial tools) on improvement. As of August 2014, a majority of recruited participants are Caucasian (87.1%) and female (85.1%) with a mean age of 42.77 (SD = 10.86) years and claiming 12 different nationalities (43% American and 25.4% Australian). Of note, and the reason for this Poster, are key issues which have emerged while conducting this study. In particular, online ethical issues have emerged related to the delivery of a self-guided adjunctive treatment to a vulnerable psychiatric population, including manage-

ment of suicidal expressions from subjects that are not local nor have been interviewed in person. MoodSwings 2.0's "red flag" system, designed to identify for further follow-up at-risk individuals during their enrollment in the study, has to date identified 5 participants with recent suicidal ideation and 36 additional participants with recent elevations on self-report measures of depression and mania. This presentation will provide a review of the limited literature on ethical concerns as they pertain to internet psychotherapy trials as well as delineation of the issues that have surfaced to date and solutions explored for handling working with patients at a distance. Given the increasing time spent online and the increased number of services moving online makes these ethical questions timely.
Conclusions: Experience of the MoodSwings 1.0 trial study suggests that internet-based psychosocial interventions have potential in the management of bipolar disorder. The online enhancements in MoodSwings 2.0, as well as a larger sample size including an attention control condition (discussion board only arm) in this study may lead to a greater understanding of these interventions as an adjunctive treatment tool. Ethical issues related to the delivery of adjunctive online psychosocial interventions for bipolar disorder involve in part balancing subject privacy concerns with prioritizing safety of individuals with bipolar disorder participating in an interactive website from international locations.
Keywords: bipolar disorder, internet, psychotherapy, ethics.
Disclosure: Nothing to Disclose.

W142. Efficacy of Cognitive Behavior Therapy and Supportive Psychotherapy for Depression in Bipolar Disorder: Neurocognitive Predictors of Treatment Response

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Background: Bipolar disorder, characterized by episodes of depression and/or mania, is a chronic and debilitating illness. Pharmacotherapy is the first line of treatment but often fails to bring patients with bipolar disorder to sustained clinical and functional remission. Although mania constitutes the hallmark of bipolar disorder, depression remains one of the most significant unresolved issues. Patients with bipolar disorder spend about 32% of the time depressed compared to about 9% with hypomanic or manic symptoms. Several adjunctive psychosocial interventions have been developed to treat bipolar disorder including cognitive-behavioral therapies (CBT), family-focused treatment (FFT), and interpersonal and social rhythm therapy (IPSRT). One of the largest randomized controlled treatment trials investigating the efficacy of psychotherapy for depression in bipolar disorder was conducted in the context of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). This study showed that FFT, IPSRT, and CBT did not differ in their efficacy of decreasing the length of time until recovery from depressive episodes (Miklowitz et al., 2007) compared to a 3-session psychoeducation intervention. It remains unclear how bipolar specific treatments compare to non-specific treatments for depression when treatments are matched on the number of sessions and attentional components. Therefore, we compared efficacy of CBT to a dose matched non-specific treatment for depression: supportive psychotherapy. In addition, we investigated neuropsychological functioning and functional brain imaging as predictors or moderators of treatment response.
Methods: Study participants were 32 patients with DSM-IV Bipolar I disorder who met criteria for a major depressive episode (16 female, CBT = 17, SP = 15) with low or no residual manic symptoms. After a clinical assessment of the severity of depressive and manic symptoms (Hamilton Rating Scale for Depression, HAM-D; Young Mania Rating Scale, YMRS), participants completed a battery of neuropsychological tests, including the Repeatable Battery of Neuropsychological Status (RBANS), the California Verbal Learning Test (CVLT), and selected subtests of the Delis Kaplan Executive Functioning System (DKEFS). In addition, the functional neuroanatomy of attention, verbal learning, and memory was assessed using two fMRI paradigms, before randomizing patient to 21 sessions of CBT for depression or supportive psychotherapy. CBT for depression was based on Otto et al., 2009. Patients in both conditions also completed mid-treatment, post-treatment, and 3-month follow-up clinical assessments.
Results: At baseline, participants in both the CBT and the SP condition exhibited moderate levels of depression (CBT: HAM-D17 $M = 20.88$, $SD = 4.05$; SP: HAM-D17 $M = 20.80$, $SD = 2.05$ between group: $t = -.072$, $df = 30$ $p = .943$). Both groups also exhibited low levels of residual manic symptoms (CBT: YMRS $M = 4.24$, $SD = 4.02$; SP: YMRS $M = 3.47$, $SD = 2.64$; between group: $t = -.629$, $df = 30$ $p = .534$). In both treatment groups, depression scores decreased significantly from baseline to mid-treatment (CBT: HAM-D $M = 10.38$, $SD = 4.77$; SP: HAM-D $M = 14.27$, $SD = 8.78$; between group stats showing no difference $df = 1$, $F = 28.79$, $p < .001$; $df = 1$, $F = .97$,$p = .335$) and from baseline towards the end of treatment (CBT: HAM-D $M = 10.85$, $SD = 4.64$; SP: HAM-D $M = 10.80$, $SD = 5.65$; $df = 1$, $F = 70.56$, $p < .001$; $df = 1$, $F = .31$, $p = .584$ between group stats showing no difference) and did not reincrease over the 3-month follow up (CBT: HAM-D $M = 9.00$, $SD = 5.91$; SP: HAM-D $M = 8.90$, $SD = 2.33$ between group stats showing no differencedf = 1, $f = 1.45$, $p = .244$; $df = 1$, $F = .19$, $p = .672$). Residual manic symptoms remained low in both groups at all assessment time points. Overall group differences between CBT and SP at all time points corresponded to a small effect size.
Conclusions: Depressed patients with bipolar disorder responded equally well to non-specific supportive psychotherapy and bipolar specific cognitive-behavior therapy for bipolar disorder. We will also present ongoing analyses regarding neuropsychological functional neuroanatomical predictors of treatment response to CBT and supportive psychotherapy.
Keywords: bipolar disorder, depression, cognitive behavior therapy, fMRI.
Disclosure: Nothing to Disclose.

W143. Epidural Cortical Stimulation of the Left DLPFC Leads to Dose-dependent Enhancement of Working Memory in Patients with MDD

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Background: Cognitive deficits are common across neuropsychiatric disorders, and a primary cause of functional disability. Nevertheless, clinicians have limited therapeutic options to facilitate cognitive enhancement, particularly of executive functions. We present results from a multicenter clinical trial of epidural cortical stimulation in patients with Major Depressive Disorder (MDD). The initial dose determination algorithm revealed acute dose-dependent facilitation of working memory function, suggesting specific therapeutic targets for device-based interventions.
Methods: Ten patients with recurrent MDD without psychotic features were enrolled. Electrodes were surgically implanted in the left DLPFC. In order to determine the stimulation parameters, an algorithm was used to assess changes in working memory, mood and anxiety as a function of parametric variations in current amplitude. The Paced Visual Serial Addition Task was used to assess working memory, and Visual Analogue Scales for "Sadness" and "Anxiety". Data were analyzed using repeated measures ANOVAs.
Results: Patients tolerated the intervention well without significant side-effects. We observed a statistically significant relationship between current amplitude and working memory performance ($p = 0.020$) and reaction times ($p = 0.035$): higher current led to improved performance and reduced reaction times. We observed a nonsignificant trend for "sadness" and "anxiety": higher current led to reduced scores for both.
Conclusions: These data highlight the relevance of the left DLPFC as a therapeutic target for cognitive enhancement in neuropsychiatric populations. In addition, it confirms the capacity of brain stimulation to improve executive function in compromised patients. Similar strategies may be effective in other clinical populations with compromised cognition, possibly with noninvasive interventions.
Keywords: Brain Stimulation, Neuromodulation, Cognitive Enhancement, Major Depressive Disorder.
Disclosure: This study is a subanalysis of data from a clinical trial sponsored by Northstar Neuroscience Inc. Northstar Neuroscience Inc. was dissolved in 2009.

W144. Analysis of Nutrient Intake and Associated Plasma Profiles in Bipolar Individuals Using Dietary and Metabolomic Measures

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Background: Dietary patterns associate with risk for depressive disorders and bipolar patients have been shown to have diets of reduced quality compared to the average population. Intake of specific nutrients, including polyunsaturated fatty acids (PUFA) correlate with bipolar incidence in global studies and the n-3 PUFA, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have shown success in alleviating depressive symptoms in bipolar subjects. However, these results are equivocal. We are interested in identifying dietary patterns that may associate with the magnitude of disease burden and treatment responsiveness in bipolar subjects to improve adjunctive treatment of this disorder.
Methods: In preliminary studies we used a 7-day diet record to monitor nutrient intake in bipolar ($n = 91$) and control subjects ($n = 75$), followed by a fasted blood draw for lipomic analysis. We also correlated dietary patterns with self-reported questionnaire scores, including the Life Functioning Questionnaire (LFQ), the Physical Health Questionnaire (PHQ), and the Short Form Health Survey (SF12).
Results: Dietary analysis confirmed significantly reduced quality diets in bipolar subjects relative to controls as summarized by the Healthy Eating Index (HEI). Intake of the n-3 PUFA, DHA and EPA; and the n-6 PUFA, arachidonic acid (AA) were also significantly reduced in bipolar subjects, after correcting for age, gender and caloric intake. Furthermore, EPA intake significantly associated with the mental health summary score on the SF-12, after correcting for age, gender, caloric intake and bipolar diagnosis. Metabolomic analysis revealed potential dysregulation of the essential n-6 PUFA, linoleic acid (LA) with significant differences in plasma levels of several LA metabolites in pro- and anti-inflammatory pathways. Finally, the use of atypical antipsychotic or antidepressant medications was also a significant factor in controlling plasma levels of several PUFA and their metabolites.
Conclusions: Taken together these data support the minimal need for therapeutic focus on improving the diet quality of bipolar patients. More research is necessary to determine the role of diet-drug interactions in controlling burden of disease measures in bipolar disorder to define specific dietary protocols that may facilitate responsiveness to treatment and improve patient outcomes.
Keywords: fatty acid, metabolomics, omega-3, omega-6.
Disclosure: Nothing to Disclose.

W145. Effect of Baseline D2/D3 Binding Potential on Functional Outcomes with DBS

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Background: Although improvements in function are fundamental to recovery from a depressive episode, evaluations related to brain activity are sparse. In order to assess the full utility of an antidepressant therapy, it is not only necessary to explore the rate of symptom decline, but also the trajectory for improvement across various domains of function. Deep Brain Stimulation (DBS) is a novel

neurosurgery for treatment resistant depression. One target being evaluated is the subcallosal cingulate gyrus, which has direct connections to the dopaminergic system, including the areas of the prefrontal cortex and limbic regions. The purpose of this study was to identify the relationship between dopamine receptor function and functional outcome with DBS at 1 year.

Methods: Following an ongoing 6-month randomized controlled trial (RCT) of sham vs. active DBS to the subcallosal cingulate gyrus in patients with treatment resistant depression ($n = 10$), patients received open-label stimulation as part of long-term follow-up. Participants who had failed at least 4 adequate antidepressant trials from different classes were enrolled in the RCT. Functional measures including the Sheehan Disability Scale (SDS) and Short Form Health Survey – 12 item (SF12) were conducted at baseline and monthly during the RCT and during long-term follow-up. Prior to surgery, patients also underwent a positron emission tomography (PET) scan to measure extrastriatal dopamine D2/D3 binding using 11C-FLB 457. The primary endpoint for this secondary analysis was 6 months of open-label stimulation (i.e. 1 year after DBS surgery).

Results: High baseline D2/D3 in the bilateral prefrontal cortex, thalamus, insula, and hippocampus correlated with lower percent change from baseline to 1 year on the SDS ($rs = -0.74$, $p = 0.014$; -0.68, $p = 0.046$; 0.74, $p = 0.014$; -0.79, $p = 0.021$, respectively). These correlations were driven primarily by changes in work functioning (all four brain regions) and social functioning (insula and prefrontal cortex only). No correlations between baseline extrastriatal dopamine binding and SF-12 were observed. The association between functional improvement and symptom change will also be discussed.

Conclusions: Dopaminergic impairment, based on high D2/D3 binding potential at baseline in limbic and frontal brain regions may be associated with poor functional improvement with DBS at 1 year. Based on the role of the prefrontal cortex, thalamus, insula, and hippocampus, the present findings could be partially explained by dopaminergic effects on sensory/motoric processing, memory and executive function as a mediator of work and social function.

Keywords: Major depression, dopamine, functional outcome, positron emission tomography.

Disclosure: The PET scan data used in this study were from a Deep Brain Stimulation clinical trial sponsored by St. Jude Medical.

W146. Light Therapy for Bipolar Depression: A Randomized, Double-blind, Parallel Placebo-control Trial

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Background: Bipolar Disorder (BD) is a major public health concern that is associated with chronic disability, lost productivity, plus increased risk for death from suicide. Although studies have uncovered effective drugs for mania, treatments for bipolar depression are few. Indicated drugs offer partial improvement at a considerable cost, including problems with intolerable side effects and elevated risks for obesity, diabetes, hyperlipidemia, and the induction of mania or rapid cycling. Investigation of light therapy for non-seasonal depression in patients with BD is compelling for several reasons: our published pilot data suggest promising antidepressant effects in patients with bipolar depression (Light Therapy for Bipolar Disorder: a Case Series in Women; Sit et al, 2007); the light "dose" can be titrated against emergent side effects; the risk for mania is low with appropriately timed light use (Sit et al, 2007); major side effects are rare; drug-drug interactions are avoided; the treatment is affordable; and wide dissemination is feasible. Building on the preliminary findings, the study objective was to confirm the efficacy of midday light treatment for depressed patients with BD Type I or II in a six-week randomized, double-blind placebo-control trial. The specific aims were to examine the change in depression levels, and the proportion of subjects who responded and remitted. We assessed predictors of response with measures of mood severity, suicidality, dosing, circadian rhythms, and expectancy. Plus, we explored possible differences in response between men and women (Exploring the Biological Contributions to Health, IOM, 2001).

Methods: We enrolled men and women between ages 18-75 with a SCID-confirmed diagnosis of BD-I or II, a current major depressive episode, and stable–dosed antimanic drug therapy. Exclusion criteria were acute psychosis; rapid cycling in the past year; obsessive compulsive disorder; alcohol or substance use disorders in the past 6 months; current hypomania, mania or mixed episode; a recent suicide attempt or active suicidal ideation; beta blockers, exogenous melatonin, or chronic NSAIDS therapy. Subjects were assigned randomly to receive active treatment (7000 lux broad spectrum light) OR the inactive comparator (50 lux dim red light) for six weeks. Following a standard dose titration protocol, subjects began with a light-dose of 15-minutes daily between NOON-2PM; weekly the dose increased by 15 minutes (if the baseline depression score had not reduced by $> 50\%$) to a target dose of 60 minutes daily. Weekly, the blinded-clinician rated mood symptoms with the Structured Interview Guide for the Hamilton Depression Scale with Atypical Depression Supplement (SIGH-ADS) and the Mania Rating Scale (MRS), plus safety and tolerability with the Scale for Suicidal Ideation (SSI) and the Systematic Assessment for Treatment Emergent Effects. Patients were evaluated for treatment response, remission and mood polarity switch at weekly visits.

Results: We evaluated 93 potential participants (71% female). Problems with rapid cycling, having mild depression only, mania or hypomania were common reasons for exclusion. We randomized 46 patients, 23 received active treatment and 23, to the inactive comparator. The baseline sociodemographic characteristics and clinical measures did not differ between groups. Thirty-eight (83%) patients completed all visits and 8 withdrew early. Of the completers, 2 stopped using the light box consistently before Week 6 (1 responder, 1 non-responder). Only two patients (4.3%) missed 1 or more study visits; both responded fully to

treatment. The primary analyses (under still blind-conditions) indicated that at baseline and Week 0, patients had moderate to severe depression levels. At baseline, the SIGH-ADS depression scores (mean + /- standard deviation) of patients assigned to treatment groups X and Y were 30.6 + 6.0 and 27.9 + 5.7, respectively ($t(44) = 1.55$, $p = 0.13$); at Week 0, the depression scores were 30.1 ± 6.1 and 26.1 ± 5.2 ($U(1) = 5.68$, $p = 0.02$), respectively. At Week 6 (final visit), the SIGH-ADS were significantly different between treatment groups; the mean depression scores of patients in group X vs Y were 17.4 ± 9.8 vs 10.4 ± 8.1, respectively ($U(1) = 6.40$ $p = 0.01$, $f = 0.41$ [large effect size]). The rate of remission (SIGH-ADS < 8) also differed significantly between groups; 14.3% (3) in group X as compared to 56.5% (13) of patients in group Y had minimal depressive symptoms by study completion ($X^2(1) = 8.46$, $p = 0.004$). Nine patients (43%) in group X as compared to 16 (70%) in group Y gained > 50% reduction in their Week 0 SIGH-ADS ($X^2(1) = 3.19$, $p = 0.07$). No one experienced a mood polarity switch. Sleep quality improved significantly across time ($t = 4.200$, $p = 8.3704x10\text{-}5$) and was associated significantly with increased daytime activity. The frequency of suicidal symptoms did not differ between groups at Weeks 0 or 6; 11 patients had any SI at Week 0, and only 5 at Week 6.

Conclusions: Original findings provide robust evidence to confirm the efficacy of midday light therapy for major depressive episodes in patients with BD. Potential benefits include low side effects, reduction in suicidal symptoms and improved sleep quality without destabilizing mood. Investigators will provide added discussion on the predictors of response upon completion of the analyses. Future research to explore brain mechanisms of response to light in BD by examining visual and neural biomarkers will be discussed (2013 NARSAD Young Investigator Award; PI: D Sit).

Keywords: Bipolar Disorder, Light Therapy, Clinical Trial, Non-Pharmacological Therapy.

Disclosure: National Institutes of Health, K23 MH 082114, Career Development Award, PI - Dorothy Sit; Clinical and Translational Science Institute, University of Pittsburgh; Brain and Behavioral Research Foundation, NARSAD 2013 Young Investigator Award. Dr. Sit received donations of study light boxes from Uplift Technologies for use in the K23 study on light therapy for bipolar depression.

W147. Neuronal and Behavioral Effects of an Implicit Priming Intervention to Reduce High-calorie Food Appeal

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Background: The prevalence of obesity in the United States has drastically increased in recent decades, creating a significant health concern. Weight loss in obese individuals is associated with a reduction in comorbid conditions, such as cardiovascular disease and hypertension. Thus, the development of novel and effective strategies that promote successful weight loss and maintenance is critical. Greater responsivity to high-calorie foods may lead to greater caloric intake, contributing to obesity. Implicit (automatic) attitudes towards food are associated with self-reported food choices and consumption. As such, altering neuronal and behavioral food cue responses by changing automatic associations may be a viable weight loss strategy. This study investigated effects of altering food perception to food cues through implicit priming (IP), in which positively or negatively valenced images were presented immediately before food images, but not consciously perceived. We hypothesize that this bottom-up sensory-level conditioning approach will alter food cue perception by modifying affective food associations. Additionally, this study used neuronal responses to food cues (using functional magnetic resonance imaging, fMRI) as a biomarker to assess intervention effects.

Methods: To investigate behavioral effects of IP, measures of "desire to eat" high- and low-calorie foods were assessed before and after either (a) an "active" implicit priming intervention or (b) a control intervention. In the active condition, images of high- and low-calorie foods were paired with implicitly presented (below perceptual threshold, for 20ms) images of either negative or positive valence (high calorie food images paired with negative; low calorie food images paired with positive), e.g., an image of ice cream implicitly primed with an image of cockroaches. The control intervention matched this, but without priming images prior to food images. Forty-two participants completed the study, with 22 in the active group and 20 in the control group. An additional 6 subjects completed active IP during fMRI to identify neuronal effects. The fMRI task included viewing food cues (high- and low-calorie) before and after IP, in a blocked design. Subjects also completed fMRI during the priming paradigm, to identify potential neuronal mechanisms involved.

Results: Visual analog scale (VAS) ratings of food pictures on "desire to eat" were completed immediately before and after the intervention. Active IP ($N = 22$) was associated with a significant decrease in high-calorie food ratings from pre- to post-IP ($t = 5.06$, $p < .001$). Furthermore, the data suggest that this response generalizes, as high-calorie images not included in the priming paradigm were also rated and showed similar rating reductions as primed images ($t = 3.77$, $p = .001$). Ratings of low-calorie foods did not significantly change. A significant interaction was observed for the comparison of high-calorie change to low-calorie change ($t = 3.88$, $p = .001$). Active IP subjects repeated the food ratings 3-5 days after the intervention. The reduction in high-calorie food ratings remained, ($t = 3.49$, $p = .006$), suggesting lasting effects. In the control group ($N = 20$), no significant changes were observed in either high- or low-calorie food ratings. Comparing active to control groups, a significant food category x session x group interaction was observed, such that significantly greater change in pre- to post-intervention ratings of high- compared to low-calorie foods was observed in the active compared to control group, $F = 6.29$, $p = .016$. Preliminary data ($N = 6$) assessing neuronal effects of active IP found the intervention to engage a similar network to that previously shown to be altered in obese-prone individuals in response to energy intake. Furthermore, IP decreased neuronal response of this network to high- compared to

low-calorie food cues, specifically in insula/inferior prefrontal cortex $p < .05$.

Conclusions: Active IP significantly reduced ratings of "desire to eat" high-calorie foods, an effect not observed in the control group. This effect was specific to high-calorie foods. That low-calorie ratings were not increased following implicit priming with positive images may be due to the likely greater salience of the negative images that were paired with high-calorie images. The negative images chosen were selected to elicit disgust, which would be expected to elicit an insula response and is commonly associated with strong evaluative conditioning effects. Indeed, preliminary fMRI results support insula activation during active IP, suggesting that the intervention is affecting the hypothesized biological target. Additionally, active IP resulted in reduced insula response to high-calorie food cues. Importantly for potential clinical use, these data support lasting effects of active IP and generalization of effects to images not specifically included in the intervention. As such, IP may represent a potential novel intervention for treatment and prevention of obesity.

Keywords: implicit priming, obesity, food preferences, fMRI.

Disclosure: Nothing to Disclose.

W148. Computer Training Associated with Persistent Improvement of Visual Processing Deficits in Schizophrenia: A Pilot Study

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Background: Visual backward masking (VBM) is a visual processing task impaired in schizophrenia [1]. Poor VBM performance in schizophrenia is associated with cognitive and functional impairments. In VBM, a brief, target visual stimulus is followed by a second stimulus, the mask. The mask disturbs accurate perception of the target stimulus. This masking effect weakens with a sufficiently long inter-stimulus interval (ISI). The deficit is so well characterized in patients with schizophrenia, healthy family members of patients, and individuals with schizotypy, that poor VBM performance is a proposed endophenotype for schizophrenia. With training, VBM can improve in healthy persons [2]. We have recently shown that VBM performance in schizophrenia can also improve with training [3], suggesting that VBM ability is not a stable trait. In our prior study, VBM training was also associated with improved visual memory in schizophrenia [3]. We describe here an extension of that study, including follow-up assessments of VBM performance months after the completion of training and the addition of a healthy comparison group.

Methods: 9 clinically stable patients with schizophrenia or schizoaffective disorder and 10 healthy volunteers received 10 sessions of VBM training over 2 months, which included 3 computer tasks: 1) a task with a target stimulus of one of 10 centrally presented letters followed by a spatially overlapping mask, 2) the same stimulus set followed by a non-overlapping mask, and 3) a location task where participants had to identify the location of target circles with spatially overlapping masks. For each task, 3 mask strengths and 13 ISI values were varied randomly to train the same range of difficulty in each participant at each session. Unmasked trials were included to control for attention and effort. The MATRICS Cognitive Consensus Battery (MCCB) was administered before and after the training. During the final session, participants were given additional VBM tasks to determine whether the training could generalize to untrained target stimuli, a new set of 10 letters. Participants were invited for a follow-up appointment 6-12 months after their training, where VBM tasks were re-administered.

Results: Repeated measures ANOVA revealed a significant main effect of training time for all three VBM tasks ($p < 0.003$) and of ISI for the overlapping mask and location tasks ($p < 0.001$). There was no significant time by diagnosis interaction for any task, suggesting that both SZ and HC may improve on this VBM task similarly. Post-hoc analysis showed statistically significant increases in performance after training in both groups. Patients' performance increased to the level of healthy controls' baseline performance. Similar to individuals with schizophrenia, healthy volunteers improved on the Brief Visuospatial Memory Test of the MCCB after the VBM training ($p < 0.02$). Performance on the untrained VBM task in the final session was significantly better than baseline performance on the trained overlapping mask task in both patients and healthy controls ($p < 0.005$ in each group), suggesting possible transfer of the VBM training to novel VBM stimuli. Patients' performance on masked trials 6-12 months after training completion was significantly better than at baseline ($p < 0.005$) and remained comparable to their performance in the final training session.

Conclusions: This pilot study demonstrates that 10 sessions of basic VBM training can improve VBM performance in schizophrenia as well as in healthy volunteers. In this small sample, VBM performance improves similarly in the two groups, and the training is associated with improvement in non-trained VBM tasks and visual memory. The improvements last at least 6 months. The small sample size is a limitation of the study. If the results are replicated in a larger trial, our results suggest that brief visual processing training in schizophrenia can result in persistent normalization of visual processing deficits. It would also support the hypothesis that memory impairment in schizophrenia may be caused in part by sensory processing impairment.

References: 1. Green MF et al (2011) Visual masking in schizophrenia: overview and theoretical implications. Schiz Bull 37:700-8. 2. Grill-Spector K et al (2000) The dynamics of object-selective activation correlate with recognition performance in humans. Nat Neurosci 3: 837-843. 3. Surti TS, Wexler BE (2012) A pilot and feasibility study of computer-based training for visual processing deficits in schizophrenia. Schiz Res 142:248-9.

Keywords: visual backward masking, schizophrenia, cognitive training, neuroplasticity.

Disclosure: Nothing to Disclose.

W149. A Novel Approach to Improve Insight into Illness and Mood in Schizophrenia Spectrum Disorders: Caloric Vestibular Stimulation

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Background: Anosognosia or impaired insight into illness is common among individuals with schizophrenia, contributing to medication non-adherence and poor treatment outcomes. Caloric vestibular simulation (CVS), which involves the infusion of cold or warm water into the external ear canal, has been shown to be an effective, albeit transient, treatment for anosognosia, somatoparaphrenia, and hemineglect in right hemisphere stroke damaged patients. Functional imaging studies demonstrate that cold CVS of the left ear activates a number of areas in the right hemisphere, including the temporoparietal junction, posterior insula, putamen, anterior cingulate, and primary somatosensory cortex. There exist a few case reports of insight improvement and mood stabilization with left cold CVS in patients with schizophrenia spectrum or bipolar disorders. As such, the aim of this study was to determine if left cold CVS would transiently improve insight into illness in schizophrenia spectrum disorders using a randomized controlled design.
Methods: Participants with a schizophrenia spectrum disorder and moderate-to-severe insight impairment (≥ 3 on the Positive and Negative Syndrome Scale Insight and Judgment item/PANSS G12) participated in a double blind, crossover, randomized controlled proof of concept study of the effects of CVS on insight into illness. Subjects sequentially received all experimental conditions—left cold (4°C) CVS, right cold CVS, and sham/body temperature—in a random order. Insight into illness was assessed using the VAGUS, Self-report and Clinician-Rated versions (VAGUS-SR and VAGUS-CR). Positive symptoms were assessed using the Schedule for the Assessment of Positive Symptoms (SAPS), and a 10-point Likert scale was used to assess mood. Assessments were performed pre-CVS, 5 min, and 30 min post-CVS.
Results: Data from 13 subjects (PANSS G12, $x = 4.5$, $SD = 1.0$) were analyzed at 30 min post-CVS. Insight into illness modestly improved with left cold CVS at 30 min (VAGUS-SR, Left cold CVS > Sham, Cohen's $d = 0.09$; VAGUS-CR, Left cold CVS > Sham, $d = 0.09$) and moderately worsened with right cold CVS (VAGUS-SR, Right cold CVS > Sham, $d = -0.31$; VAGUS-CR, Right cold CVS > Sham, $d = -0.05$). This difference was most prominent when comparing left cold to right cold CVS (VAGUS-SR, Left > Right cold CVS, $d = 0.40$; VAGUS-CR, Left > Right cold CVS, $d = 0.13$). Left cold CVS was also had a strong effect on improvement in mood (Left cold CVS > Sham, $d = 0.88$; Right cold CVS > Sham, $d = 0.07$; and Left > Right cold CVS $d = 0.92$).
Conclusions: Left cold CVS appears to transiently improve insight into illness and elevate mood in schizophrenia spectrum disorders. The procedure's effectiveness is thought to be due to the stimulation of under active right hemisphere circuits via vestibular nuclei projections to the contralateral hemisphere when using left cold CVS. Treatment studies over an extended duration of time (e.g. daily x 5 - 10 days) are required to determine the procedure's efficacy for improving illness awareness in schizophrenia spectrum disorders.
Keywords: Brain stimulation, Vestibular stimulation, Insight, Schizophrenia.
Disclosure: Nothing to Disclose.

W150. Functional and Anatomical Connectivity of Individual Deep Brain Stimulation (DBS) Contacts in Patients with Movement Disorders Correlate with Clinical Outcome

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Background: Prediction of therapeutic response to deep brain stimulation (DBS) for Parkinson's disease with motor fluctuations and disabling essential tremor remains largely empirical, in part because it is unclear what are the circuits that need to be engaged by DBS to achieve clinical benefit in each case.
Methods: We used probabilistic DTI tractography and DBS-triggered event related potentials on surface electroencephalography (DBS-ERP) to trace the connections of DBS leads in individual patients and correlate them to clinical outcomes of DBS. We collected data from 70 patients who underwent DBS surgery for Parkinson's disease or disabling essential tremor, obtained MRI images as part of the surgical planning including FLAIR, contrasted T1,T2 and DTI images (64 directions) on a 3T Phillips scanner. Images were merged with the postoperative CT scan to identify the exact electrode placement. Following reconstruction, manual tracing of ROIs (involving the DBS lead active contacts) was performed on nonsegmented high resolution T1 images corregistered into T2 space with the post-op CT using BRAINLAB software (Feldkirchen, Germany). Images were realigned using the plane containing the anterior and posterior commissures and the sagittal sulcus to correct head tilt, and resampled into isotropic voxels (0.9375 mm3). Fractional anisotropy for each voxel was calculated for each volume. DBS-ERP were then obtained from each monopolar configuration and source analysis was performed with SLORETA (Asalab, ANT Neuro, Enschede, Netherlands).
Results: Connectivity measures were correlated with clinical outcome from DBS and programming data. Involvement of connections to both the primary motor cortex and supplementary motor area predicts better outcomes than projection to either structure alone. Projection to additional structures correlates with side effects.
Conclusions: Our data show an example of how connectivity data can be used to improve outcomes of DBS.
Keywords: DBS, tractography, movement disorders, event related potentials.
Disclosure: Nothing to Disclose.

W151. Cognitive Predictors of Initial Auditory Training Improvement in Schizophrenia Patients

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Background: Targeted Cognitive Training (TCT) has shown great promise for remediating cognitive deficits in patients with schizophrenia (SZ). One component of this computerized intervention uses adaptive and reinforcing auditory frequency discrimination (AFD) exercises aimed at improving the fidelity of basic auditory processing. This training places progressively increasing demands on auditory perception, attention, and working memory leading to neuroplastic changes that "feed forward" to impact the neural networks that subserve higher-order cognition. Although TCT appears to produce robust improvements in global cognition at the group level, nearly half of chronic SZ patients fail to derive a meaningful benefit from the intervention, underscoring the need to identify early predictors of therapeutic response. Since TCT relies heavily on auditory attention and working memory – domains commonly impaired in SZ – we hypothesized that performance in those cognitive domains would be related to AFD improvements during the initial exposure to training.
Methods: Schizophrenia outpatients ($n = 37$) underwent neurocognitive testing, including measures of auditory attention and working memory (Letter Number Sequencing, Forward and Re-ordering Conditions) followed by one hour of TCT (BrainHQ, www.positscience.com). Performance metrics generated from TCT included pre-training auditory processing speed and percent improvement after training.
Results: Auditory attention and auditory working memory were significantly associated with pre-training auditory processing speed ($r = -0.61$ and $r = -0.45$, respectively, [$p's < 0.01$]). In contrast to our expectations, improvements in auditory processing accrued during the training session were not associated with any pre-training cognitive abilities.
Conclusions: Patients with relative deficits in the auditory-dependent cognitive domains "targeted" by TCT appear to exhibit initial rates of improvement comparable to those of less cognitively impaired patients. Additional studies are necessary to identify predictive biomarkers of cognitive response to therapeutic doses of TCT in SZ patients.
Keywords: schizophrenia, cognition, cognitive remediation, auditory processing.
Disclosure: Dr. Light has served as a consultant for Astellas, Forum, and Neuroverse. Dr. Swerdlow has been a consultant for Genco Sciences, Ltd.

W152. Psychometabolomics: Assessment of Treatment-Refractory Depression

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Background: Inborn errors of metabolism may present as a spectrum ranging from neonatal lethality to non-specific symptoms. Milder central nervous system specific inborn errors of metabolism may also present with isolated psychiatric symptoms, including severe depression. Treatment refractory depression is a devastating clinical problem with significant morbidity, mortality, and cost to society. We recently published a report of a young adult with severe, unremitting depression and multiple suicide attempts who did not respond to pharmacotherapy or electro-convulsive therapy (ECT). Further evaluation identified a severe deficiency of all cerebrospinal fluid (CSF) metabolites of biopterin, a critical cofactor for synthesis of the monoamine neurotransmitters, suggesting a variant of guanosine triphosphate (GTP)-cyclohydroxylase deficiency. Treatment with the biopterin analogue sapropterin led to a dramatic remission of his depression. His recovery was the impetus for this study.
Methods: We performed an extensive neurometabolic evaluation for adolescent and young adult patients with depression refractory to at least three maximum dose treatment trials. Plasma and urine testing were performed per standard protocols including gas chromatography-mass spectrometry, tandem mass spectrometry, and high pressure liquid chromatography profiling of blood and urine to examine known groups of metabolites contributing to psychiatric symptoms. A lumbar puncture for CSF collection also allowed for the identification of any new variants of known disorders. Specific metabolic panels for analysis are available clinical measures with established normal ranges from a protocol for assessment of neuropsychiatric symptoms in inborn errors of metabolism developed by Drs. Vockley and Pan, and include: Blood: Amino acids, Acylcarnitine profile, Lactic acid, Phenylalanine, Ammonia, Lysosomal WBC enzymes with mucopolysaccharides, very long chain fatty acids, Transferrin electrophoresis for glycosylation defects, Chromosome microarray analysis, Fragile X, serotonin, folate, B12, B6. Urine: Organic Acids, Amino Acids, Purines and pyrimidines, Creatine/Guanidinoacetate analysis, urinalysis CSF: Amino acids, Glucose, Lactate, Homovanillic Acid, Biopterin, Neopterin, 5-hydroxyindoleacetic acid, 5-methyltetrahydrofolate, 3-o-methyldopa (3-OMD), Alpha-aminoadipic semialdehyde.
Results: In an exploratory trial triggered by this patient we have now identified evidence of underlying central nervous system (CNS) neurometabolic disorders in 13 of 20 additional patients with treatment refractory depression. Nine of these patients have cerebral folate deficiency and treatment with folinic acid has resulted in sustained improvement of depressive symptoms in all who have had greater than one month of treatment. Notably, none of the current tools aimed at developing personalized strategies for the treatment of depression (e.g., functional neuroimaging or pharmacogenetics) would have identified these defects or led to effective therapy.
Conclusions: The examination of the role of CNS-specific metabolomic disorders in disease pathophysiology in adolescents and young adults with a history of severe, treatment refractory depression is indicated. Recommendations for such examination are discussed. We hypothesize that such disorders are under-recognized in this patient population. Identification and intervention could result in life-changing and life-saving treatment of severe depression.

Keywords: psychometabolomics, cerebral folate deficiency, tetrahydrobiopterin, depression.
Disclosure: Nothing to Disclose.

W153. F17464, a Selective Dopamine D3 Antagonist/ Serotonin 5-HT1A Partial Agonist, as a Clinical Candidate with Wide Ranging Antipsychotic-like Activity in Models of Dopamine and Glutamate Dysfunctions

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Background: The dopamine theory of schizophrenia, originating from the discovery of anti-dopaminergic property of antipsychotic drugs, is still valid and has received confirmation by PET and functional imaging studies. More recently, evidence for glutamate dysfunctions in schizophrenia have emerged, but the clinical development of drugs targeting glutamate, such as pomeglumetad or bitopertine, has been discontinued for lack of efficacy. Drugs acting selectively at dopamine D3 receptor may target both dopamine and glutamate dysfunctions.
Methods: A novel antipsychotic candidate, F17464, has been characterized in vitro and in vivo at dopamine and non-dopamine receptors. The ability of this compound to overcome both dopamine and glutamate dysfunctions has been studied in animals receiving amphetamine, a dopamine-releasing agent, and MK-801, an NMDA receptor blocker, respectively, and compared to a variety of antipsychotic drugs. Then, PET studies with non human primate monkeys and human healthy subjects, and Phase 1 clinical trial were performed.
Results: F17464 has a high affinity for human recombinant dopamine hD3 receptors (Ki = 0.17 nM), and lower affinity for hD2 (Ki = 12.1 nM) and is an antagonist. It is a full D3 antagonist and has a very low intrinsic activity at D2 receptors (8% of that of dopamine). F17464 also has a high affinity for serotonin 5-HT1A receptors (Ki = 0.16 nM) and is a partial agonist. F17464 increases dopamine metabolites levels in the limbic forebrain and prefrontal cortex (PFC) and dopamine extracellular levels in the PFC. F17464 blocks amphetamine- and MK-801-induced hyperactivity at doses that produce no or little effects on spontaneous activity. F17464 reverses MK-801-induced deficit in social interactions, displays a weak anxiolytic activity, and possesses a procognitive profile in various preclinical tests. All the effects produced by F17464 in rodents are in the 0.16-2.5 mg/kg dose range, which corresponds to plasma exposure in non human primates giving extensive and selective D3 receptor occupancy as measured by PET with [11C](+)-PHNO. In human healthy subjects, the extensive, selective and long-lasting D3 receptor occupancy was confirmed by PET. In Phase 1 studies, after single or repeated doses, F17464 has a good safety profile: it exhibits sparse, generally mild and not dose-related adverse events, no EPS, and mild and dose-related increased prolactinemia.
Conclusions: In spite of having a very weak anti-D2 activity, the D3 antagonist/5-HT1A partial agonist F17464 displays a wide ranging preclinical antipsychotic profile similar to that of antipsychotic drugs, but without any deleterious effects, such as sedation or amnesic effects. In addition, it has a preclinical procognitive profile and a good safety profile in human healthy volunteers. F17464 has entered Phase 2a clinical trial, designed to assess its efficacy and safety compared to placebo in monotherapy in patients with acute schizophrenia, during a 6-week treatment.
Keywords: Schizophrenia, PET study, Phase 1.
Disclosure: I am a full-time employees at Pierre Fabre Research Institute and minor shareholder of Pierre Fabre SA equity.

W154. Schizconnect: Large-scale Schizophrenia Neuroimaging Data Integration and Sharing

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Background: Schizophrenia is a heterogeneous, complex disease. Increasingly, data are needed from large samples that are often beyond the capability of any individual research group. Consortia efforts such as the Functional Biomedical Informatics Research Network (FBIRN), the MIND Clinical Imaging Consortium (MCIC) and others have allowed the exploration of multi-site datasets that have improved our understanding of schizophrenia. However, formidable technical barriers prevent further contributions to these databases, which would require manually matching variables across datasets (i.e., ontological match), manually transferring data, or converting existing datasets to a different architecture. These options are not ideal and costly in part due to the manual and idiosyncratic steps that need to be replicated for every new study. We present SchizConnect, an on-going project that builds upon the existing consortia to establish a large-scale neuroimaging data federation resource for schizophrenia research. It overcomes the above barriers, and allows for querying and combing of neuroimaging data from different databases to form compatible mega-datasets.
Methods: The SchizConnect architecture has 3 components: 1) The data sources – individual databases with idiosyncratic platforms and interfaces, each containing compatible variables but with varying names and descriptions. Current 3 are: Northwestern University Schizophrenia Data and Software Tool (NUSDAST, http://www.nitrc.org/projects/nusdast), FBIRN (http://fbirnbdr.nbirn.net:8080/BDR), and MCIC/COBRE (http://coins.mrn.org/dx). 2) The SchizConnect Mediator – the data integration engine, containing a common data model (including common relations and ontological terms) that mediates compatible data across the different data sources. 3) The SchizConnect.org web portal, which provides a user-friendly interface for data query and download. At http://SchizConnect.org, the user can build a query using a graphical user interface (GUI). They are passed to the Mediator as an SQL query expressed on the common data model terms. The Mediator translates this

SQL into the schemas of the data sources, and then queries each data source directly. The queries to the FBIRN and NUSDAST, each stored in a distinct database platform, are returned to the Mediator in distinct formats. MCIC/COBRE data required special handling because the native database architecture did not allow for actual data to be returned to the Mediator. We therefore extracted common model-defined variables from MCIC/COBRE via an application program interface (API) and stored in a local database at the Mediator site, which is then queried with its own return format. Returns from queries to these different data sources are then collated and presented to the user as a unified table that includes provenance using mediated common data model terms. SchizConnect.org interacts with the user for signing of data use agreements (DUAs) and downloading data. Downloading FBIRN is done via gridFTP, NUSDAST via REST API, MCIC/COBRE via HTTP.
1U01MH097435 1R01MH084803 P50MH071616 R01MH056584 U24RR025736-01 U24RR021992 U24GM10420 P20GM103472.
Results: Currently, 1,120 subjects with neuroimaging data and non-imaging meta-data from the 3 data sources are accessible at SchizConnect. Neuroimaging data contains 1.5T and 3T structural and functional scans collected on a variety of scanner platforms. Demographics data contains age and gender information. The SchizConnect common domain models currently include subject, imaging protocol, scanner protocol, and diagnosis models. The subject model mediates compatible variables from the data sources pertaining to age and gender. The imaging protocol model mediates compatible variables pertaining to MR scans, including T1, T2, MPRAGE for structural and resting state, task paradigm, working memory for functional scans. The scanner protocol model mediates compatible variables pertaining to scanner field strength, vendor and model. The diagnosis model mediates compatible variables pertaining to schizophrenia-related group designation, including schizophrenia-broad, schizophrenia-strict, schizoaffective and no-known diagnosis. GUI queries are built by drag-and-dropping of "subject" and "MRI (imaging/scanner)" constructs, each allowing for filtering on mediated variables. Constructs can be concatenated by a series of logical and's and or's to form a query such as "1.5T T1-weighted scans of male subjects 40 years or younger." The above query returns 857 downloadable images from the FBIRN and NUSDAST databases. SchizConnect provides both summary and subject-level information/data. Unregistered users (i.e., anyone accessing the web portal can obtain summary counts of downloadable images for each query. Registered users can receive detailed information about each returned result and can download data after signing the DUAs. The imaging data resulting from the queries are first transferred out of the data sources and warehoused at SchizConnect.org host together with the mediated meta-data table for a specified limited time period for downloading. Links to these files along with unpacking instructions are sent to the user via email and are available through the "MySchizConnect" page of the website.
Conclusions: These initial results demonstrate that SchizConnect allows mediation and combining of neuroimaging data from different databases to form compatible mega-datasets with accuracy and fidelity. In SchizConnect, data remains at the sources. Providers maintain control of their data and do not need to modify them. The user's query addresses all the datasets, avoiding the need to directly interact with each provider. The web portal is user-friendly and intuitive, performing query and download from each data source in real-time, but appearing to the user as a single, virtual database with a well-defined consistent schema to the user. As an on-going project, we have begun to define additional common data model terms for cognitive and psychopathological domain variables, make available additional imaging modalities and subjects, and identify and evaluate potential new data sources. SchizConnect shows considerable potential for overcoming current barriers for creating large-scale datasets to increase statistical power, accelerating the testing of new hypotheses and methods, and creating a resource for developing advanced techniques to better integrate disparate data.
Keywords: Data mediation and integration, neuroinformatics, mega analysis, schizophrenia databases.
Disclosure: Nothing to Disclose.

W155. Cannabis Withdrawal in Adults with Mood Disorders

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Background: Cannabis is used annually by 119-224 million people globally. Approximately 14% are daily users; 10% of regular users become dependent. The objective of this study was to compare the experience of cannabis withdrawal in adults before (pre-mood disorder) and after their development of a mood disorder.
Methods: The study was conducted at psychiatric facilities in the Baltimore, MD area affiliated with the Maryland Psychiatric Research Center. Participants were a convenience sample recruited by study staff or referred by the treating clinician. Adults with current mood disorder ($N = 62$) completed the Marijuana Quit Questionnaire (MJQQ), a 176-item, semi-structured questionnaire assessing sociodemographic characteristics, cannabis use patterns, and experience of cannabis withdrawal during their self-defined "most difficult" cannabis quit attempt made without formal treatment while not in a controlled environment. Fifty-eight participants provided complete data. A clear order of onset between start of their index quit attempt and diagnosis of mood disorder was reported by 53 participants, who were included in analyses.
Results: Twenty nine participants had major depression (16 mood, 13 pre-mood); and 24 participants had bipolar disorder (18 mood, 6 pre-mood), resulting in 34 participants in the mood disorder group and 19 in the pre-mood disorder group. The average age and sex of participants with mood disorder and pre-mood disorder at the start of the index quit attempt was 43 and 49 years and 68% and 32% men, respectively. The majority of participants in both groups were African-American (74% and 79%, respectively). The most important reason given for quitting

cannabis use was not wanting to be a bad example for their children (17.7%) in the mood disorder group and liking themselves better if they quit (15.8%) in the pre-mood disorder group. Withdrawal symptoms of physical discomfort (6% vs. 26%, $p = 0.04$), sweating (12% vs. 37, $p = 0.03$), tremor (12% vs. 32%, $p = 0.08$), and vivid dreams (24% vs. 47%, $p = 0.07$) were less prevalent in the mood disorder group than in the pre-mood disorder group. There was no significant group difference in prevalence of DSM-5 cannabis withdrawal syndrome: 70.6% in the mood and 84.2% in the pre-mood disorder group. There were no significant group differences in the proportion of participants who used cannabis (26% vs. 38%), tobacco (79% vs. 50%), or alcohol (68% vs. 41%) to cope with their cannabis withdrawal experience. All participants gave consistent responses to four pairs of mutually exclusive questions on withdrawal symptoms; all but one participant gave consistent responses to a pair of questions on duration of abstinence during their quit attempt. This consistency suggests the internal validity of participants' self-report.
Conclusions: Among 53 adult cannabis users with mood disorder, there were few significant differences in cannabis use history or experience of cannabis withdrawal between those whose quit attempt occurred after (mood disorder) or before mood disorder (pre-mood disorder) onset, except that withdrawal symptoms of physical discomfort and sweating were significantly less prevalent in the mood disorder group. In both groups, cannabis withdrawal can serve as negative reinforcement for relapse to cannabis use. These findings suggest that cannabis withdrawal is clinically significant in people with mood disorders. Future research is warranted to validate these findings in a longitudinal study with a larger sample.
Keywords: Cannabis, Mood.
Disclosure: Nothing to Disclose.

W156. Damage-associated Molecular Patterns in Bipolar Disorder

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Background: There is a growing body evidence showing patters of immune activation in patients with Bipolar Disorder (BD). Damage-associate molecular patterns (DAMPs) are part of the sterile immune activation reaction. The aim of the present study was to assess serum levels of DAMPs (represented here by circulating cell free (ccf) DNA, Heat Shock Protein (HSP)70, HSP90□, and HSP60, and cytochrome C) in drug-free BD patients during acute episodes and after remission. Two control groups were included: healthy subjects (negative control) and patients with sepsis (positive control of immune activation).
Methods: Patients with BD ($n = 20$) were recruited from subjects treated at the Bipolar Disorders Program of Clinical Hospital of Porto Alegre and University Hospital of Santa Maria, both in Southern Brazil. Manic and depressive symptoms were assessed using the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale, 21-item version (HDRS-21). All participants provided written informed consent (which was approved by the local ethics committee) after the nature of the procedures had been fully explained.
Results: At baseline bipolar patients differed from controls in the levels of ccf nDNA ($F = 7.973$, $p = 0.009$) and HSP90□ ($F = 4.32$, $p = 0.046$). In order to summarize the shared variance of DAMPs associated with immune activation in the different groups, we used the first component (from a principal component analysis) extracted from the positive control group. This component was called "apoptosis". Bartlett's test was significant ($p = 0.001$), indicating factorability. Significant differences were found in the apoptosis component between negative control vs BD baseline ($p = 0.022$) as well as negative control vs positive control ($p < 0.0001$).
Conclusions: The findings showed an increase in DAMPs levels in bipolar patients. In addition, the results showed that DAMPs levels may decrease after remission, indicating that part of the immune activation observed in BD is related to the acute phase of illness.
Keywords: Bipola Disorder, Inflammation, DAMPs.
Disclosure: Nothing to Disclose.

W157. Blood Biomarkers of Behavioral Resilience and Treatment Response in the Mouse Chronic Social Defeat Stress Model of Depression

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Background: The chronic social defeat stress model, which results in susceptible and resilient mice with and without depression-like deficits, has been used to explore biological mechanisms underlying risk of depression, the interplay between risk and triggering factors, and response to antidepressant agents. Potential for translation to humans has been demonstrated in studies of postmortem brain tissue from patients with Major Depressive Disorder (MDD). Translational models are needed not just to understand brain mechanisms behind the development and treatment of MDD, but also to identify blood-based biomarkers that could be applied to a human population to elucidate depression risk, disease subtype, and prediction of treatment response. In this work, we explore blood mRNA and miRNA biomarkers in mice predictive of phenotype and treatment response at baseline, post-stress, and post-treatment.
Methods: In this study, 120 C57/BJ mice were subjected to 10 days of chronic social defeat stress and then treated with saline, chronic imipramine, or acute ketamine. Blood was drawn at baseline, post stress (day 12), and after treatment (day 28). mRNA expression levels were determined for 230

hypothesis-based genes using the Nanostring nCounter platform and miRNA on the Nanostring miRNA Expression Assay. A machine learning approach was applied which included gene-clustering, feature selection, and classification to identify expression patterns which classified mice as susceptible or resilient to defeat. Due to large differences in group size, we also used a gene-wise interaction model with significance calculated via permutations and moderated-t statistics.

Results: Following chronic social defeat stress, 61 mice were classified as susceptible and 47 as resilient. For biomarker analysis, mice with more extreme phenotypes were selected (susceptible, n = 42 resilient, n = 9) as well as 10 control mice. The predictive power for phenotype was highest using 10 clusters (47 genes total) measured at day 0, or 10 clusters (36 genes) that changed from day 0 to day 12 (both with Accuracy = 82.25%, Sensitivity = 80.95%, Specificity = 88.89%). Twelve genes were common to both models. Blood mRNA biomarkers measured at day 12 were not predictive. Among biomarkers at day 0, the top ranked cluster was comprised of BDNF and CCBL1/KAT1, which were expressed at lower levels in susceptible mice at baseline. The second-ranked cluster was comprised of CRTC2, NR1B1, RPS6KA3, TXNIP and VIM, all expressed at a higher level in susceptible mice. For mRNA biomarkers that changed from day 0 to day 12, the top two clusters (cluster 1: CD8A, CD8B, MAP2K1, CTSS; cluster 2: MYST2/KAT7, HDAC2, SMARCA4) decreased in expression in susceptible mice as a result of chronic social defeat, while remaining the same for resilient mice. The third cluster (KDM4B, BAZ2A) was unchanged in susceptible but decreased in expression in resilient mice. Top mRNA markers for treatment response to ketamine or imipramine did not overlap. Among significant mRNAs at day 0, lower TXNIP levels at day 12 predicted response to ketamine. miRNAs were most predictive at day 12. The most significant was miR-365, which was higher in resilient mice at day 12. This miR, together with genes that exhibited a differential change in expression as a result of social defeat, forms part of a tightly interconnected network centered on interleukin-6.

Conclusions: In this hypothesis-driven biomarker exploration study, several, but not all, previously suspected genes and pathways have been replicated, and many of the genes above have been implicated in MDD and other psychiatric illnesses as risk or disease biomarkers. It is counterintuitive that predictive power of the current phenotype (at day 12) is weaker than our ability to predict future phenotype (at day 0) and is possibly the result of the small study size. However, taken at face value, it suggests that in the study of biomarkers among currently depressed subjects, factoring in available data around risk factors may improve performance. In looking towards biomarkers translatable to human subjects suffering from MDD, findings should be further investigated in other animal models of depression, in human resilience studies of high-risk patients, and in depressed patients.

Keywords: Depression, Biomarker, Ketamine, Antidepressants.

Disclosure: Empoyees of Janssen R & D, LLC., or Transcription Diagnostics Inc. Work was funded by Janssen R&D, LLC.

W158. Effect of Optogenetic Inhibition of a Lateral Orbitofrontal to Basolateral Amygdala Subcircuit on Cue-induced Cocaine-seeking Behavior in Rats

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Background: Drug-addiction is a chronic relapsing disorder that is characterized by compulsive drug-seeking and –taking behavior even after prolonged periods of abstinence. Relapse prevention is a key treatment challenge because relapse can be triggered by multiple drug-associated cues and recruits multiple brain circuits. The lateral orbitofrontal cortex (lOFC) and basolateral amygdala (BLA) are two brain regions that are theorized to play a critical role in drug relapse given that they are engaged in both adaptive and maladaptive forms of associative learning. In rodents, neural activity in the lOFC and BLA is required for CS-induced drug-seeking and functional disconnection of lOFC-BLA circuits impairs drug context-induced cocaine-seeking behavior. However, it has not been investigated whether monosynaptic connections between these brain regions are necessary for this phenomenon. The specific objective of the present study was to determine whether neural activity within monosynaptic lOFC → BLA subcircuits is necessary for CS-induced cocaine-seeking behavior.

Methods: In Exp. 1, in order to study the lOFC → BLA subcircuit, we virally overexpressed a light-activated ion pump, enhanced Natronomonas pharaonis halorhodopsin-mCherry (eNpHR3.0-mCherry), in lOFC neurons that project to the BLA. We utilized an adeno-associated viral (AAV) vector expressing a Cre-dependent, double-floxed (DIO) eNpHR3.0 fused to an mCherry reporter (AAV-DIO-eNpHR3.0-mCherry). To induce recombination and expression of eNpHR3.0, we infused AAV-DIO-eNpHR3.0-mCherry into the lOFC plus a retro-Cre-GFP into the BLA. To examine whether expression was Cre-dependent, control rats received only DIO-eNpHR3.0-mCherry into the lOFC. In Exp. 2, rats received retro-Cre-GFP into the BLA plus DIO-eNpHR3.0-mCherry (or control mCherry) as well as optic fiber placement into the lOFC. A second group of rats received retro-Cre-GFP into the BLA plus DIO-Arch-YFP (a light activated enhanced proton pump) or control YFP as well as optic fiber placement into the lOFC. Rats were trained to self-administer cocaine infusions paired with a light + tone CS during 10 daily 2 hr sessions, followed by extinction training. Rats were then tested for CS-induced reinstatement of cocaine-seeking behavior. During the test session, response-contingent CS presentation was coupled with laser stimulation into the lOFC or no laser stimulation, in a counter-balanced order across two test days.

Results: In Exp. 1, we observed robust expression of eNpHR3.0-mCherry in the lOFC with < 1 mm spread of virus from the injection site and no expression in the BLA. Furthermore, rats that received eNpHR3.0-mCherry only (with no retro-Cre-GFP into the BLA) had no expression of eNpHR3.0-mCherry in the lOFC. Lastly, eNpHR3.0-mCherry expression was primarily observed in excitatory glutamatergic projection neurons, as indicated by a high degree of co-localization between eNpHR3.0-mCherry and the excitatory marker calcium/calmodulin-dependent protein

kinase II. In Exp. 2, preliminary data suggest that optogenetic inhibition (i.e. laser ON) in rats that had received retro-Cre-GFP into the BLA plus DIO-eNpHR3.0-mCherry into the lOFC, attenuated the ability of the CS to reinstate cocaine-seeking behavior relative to responding observed without laser stimulation (laser OFF). Conversely, optogenetic inhibition in rats that had received retro-Cre-GFP into the BLA plus DIO-Arch3.0-YFP into the lOFC failed to alter cocaine-seeking behavior. This discrepancy in findings may be due to recombination and expression of DIO-Arch3.0-YFP in a different lOFC neuronal population compared to DIO-eNpHR3.0-mCherry. Future studies will be conducted to determine the importance of the BLA→lOFC subcircuit in CS-induced cocaine-seeking behavior.
Conclusions: This novel line of studies investigates the contribution of monosynaptic connections between the lOFC and BLA to CS-induced reinstatement of cocaine-seeking behavior. Mapping functionally significant monosynaptic connections between the lOFC and BLA at the subcircuit level may yield fundamental information about the drug relapse circuitry. Furthermore, these studies may provide essential information for the development of effective treatments for cocaine addiction.
Keywords: optogenetics, cue reinstatement, lateral orbitofrontal cortex, basolateral amygdala.
Disclosure: Nothing to Disclose.

W159. Pharmacogenomics of SSRI Treatment Response: Findings of the International SSRI Pharmacogenomics Consortium (ISPC)

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Background: Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used medication class for major depressive disorder. However, response to SSRI treatment varies considerably between patients. It is widely recognized that identification of pharmacogenetic predictors of drug response has great potential to improve the treatment of MDD.
Methods: The International SSRI Pharmacogenomics Consortium (ISPC) was established to investigate the genetic factors contributing to variable response to SSRIs. Seven sites from Europe, North America and Asia contributed clinical phenotypic data and DNA samples to the ISPC. Demographic and clinical data were curated (i.e. collected, formatted, and subjected to quality control) by staff at the Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB, www.pharmgkb.org), and genotyping was performed at the RIKEN Center for Integrative Medical Sciences (Yokohama, Japan) using Human Omni Express BeadChips and an exome chip. After data quality control, 647,024 genotyped single nucleotide polymorphisms (SNPs) and almost 7 million imputed SNPs were analyzed. The genome-wide pharmacogenomic analysis focused on treatment outcomes at 4 weeks, measured using the 17-item Hamilton Rating Scale for Depression (HRSD-17), analyzed in 885 subjects with available clinical and genetic data. The two primary outcome phenotypes were % change in HRSD-17 score during the first 4 weeks of treatment (%ΔHRSD) and 'response' (defined as $\geq$ 50% reduction in HRSD-17 score from baseline to 4-week visit). Data from two prior GWAS of SSRI response, the Mayo Clinic Pharmacogenomic Research Network Antidepressant Medication Pharmacogenomics Study (PGRN-AMPS) and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, were used for replication analysis, and a meta-analysis of the three studies was performed. Finally, we investigated the association of clinical response with several SNPs that showed genome-wide or suggestive evidence of association in prior large pharmacogenomic studies of antidepressants.
Results: In the ISPC data, top association signals included SNPs in the gene VWA5B1 (von Willebrand factor A domain containing 5B1) in the analysis of %ΔHRSD (rs56058016; p = 1.13E-07), and SNPs in the gene NCKAP1L in the analysis of response (rs3782401; p = 7.03E-07). In the meta-analysis of ISPC with PGRN-AMPS and STAR*D, one SNP in the HPRTP4 (hypoxanthine phosphoribosyltransferase pseudogene 4) gene approached genome-wide significance for the 'response' phenotype (rs2456568, p = 5.03E-08). Other top signals, which did not reach genome-wide significance, included SNPs in potentially relevant candidate genes, including MCPH1 (microcephalin 1), STK39 (serine threonine kinase 39), and RYR3 (ryanodine receptor 3). The top 10 association signals in the ISPC data did not replicate in the PGRN-AMPS or STAR*D analyses. Analyses of SNPs identified in prior pharmacogenomics analyses of antidepressants demonstrated nominal evidence for association of % change in depression score with SNP rs11624702 in the gene MDGA2 (MAM domain containing glycosylphosphatidylinositol anchor 2), both in the ISPC data and in the meta-analysis with PGRN-AMPS and STAR*D.
Conclusions: Although the present findings do not provide evidence for specific genetic factors that markedly affect clinical response to SSRI treatment in major depression, there is need for closer exploration of genes showing the most marked associations. Ongoing efforts are focused on pathway analyses and investigation of pharmacogenomics predictors of outcomes in more refined and homogeneous patient subsamples.
Keywords: pharmacogenomics, SSRI, major depressive disorder, genome-wide association study.
Disclosure: Dr. Teri E Klein is a stockholder and scientific consultant to Personalis Inc.

W160. Early Stage Assessment of the Abuse Potential of Centanafadine, a Triple Reuptake Inhibitor: Preclinical and Clinical Study Results:

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Background: Compounds that increase dopamine (DA) levels in the nucleus accumbens are potentially euphori-

genic and have recognized abuse liability, including stimulants like cocaine, amphetamines, and methylphenidate. Amphetamine and methylphenidate are used in the pharmacotherapy of attention-deficit hyperactivity disorder (ADHD), but their abuse liability represents a potential safety issue. Recently, triple reuptake inhibitors (TRIs) have been considered for use in ADHD because they inhibit reuptake of norepinephrine (NE) and DA, neurotransmitters known to mediate the symptoms of inattention, impulsivity and hyperactivity in ADHD. Since these drugs increase DA in the nucleus accumbens, there is the possibility that they could have abuse liability. In this regard, two drugs from this class, tesofensine and GSK372475/NS2359, have been investigated in human abuse liability studies in recreational stimulant users and have shown little or no abuse potential. Centanafadine (CTN, EB-1020) is a NE > DA > 5-HT preferring TRI being developed for the treatment of ADHD in adults. In consideration of its ability to increase DA, the abuse potential of CTN is undergoing a careful evaluation. Here, we discuss preclinical and clinical studies in relation to the abuse potential of CTN conducted to date, using the draft FDA drug abuse potential assessment decision tree (2011) as a framework.
Methods: Preclinical Pharmacology. Interaction with off-target receptors associated with drug abuse was performed using standard radioligand binding assays. An in vivo microdialysis study was conducted in conscious rats to evaluate elevations in monoamine levels following administration of CTN (3 mg/kg, ip). Locomotor activity was evaluated in mice following administration of CTN (20 and 40 mg/kg po). Clinical Trial Data Relative to Abuse and Dependence Potential. A review and analysis of treatment emergent adverse events (TEAEs) of completed Phase 1 and Phase 2 clinical trials was conducted. The search was used to examine TEAEs that are potentially indicative of abuse potential (eg, ''euphoria''), but also to examine pharmacologic effects of interest specific for the therapeutic class (eg, stimulant-like effects). The following terms formed the basis of the search: euphoric mood, agitation, inappropriate affect, feeling drunk, hallucination (auditory, visual, and all subtypes).
Results: Preclinical Pharmacology. CTN had low affinity (IC50 > 3 μM) for a panel of receptors associated with drug abuse potential. The microdialysis study in rats showed that CTN at a pharmacological dose shown to be active in an animal model of ADHD, increased extracellular NE, DA, and 5-HT to 237%, 194%, and 174% of baseline in prefrontal cortex, respectively, and DA to □425% of baseline in striatum. Unlike stimulants, which increase locomotor activity, CTN significantly decreased mouse locomotor activity to 38% and 49% of saline control levels at 1 hour post-dose. Clinical Trial Data. Single IR doses up to 800 mg and multiple daily doses up to 500 mg (IR or SR) have been administered in clinical trials. There were no TEAEs in the Phase 1 and 2 studies associated with abuse or misuse. In the Phase 1 studies (N = 36), mild euphoric mood was reported by 2 subjects (6%, both at 800 mg). These events were considered possibly related or related to investigational product and considered mild by the investigator. Both of these events were also associated with aversive effects. Energy increased was reported by 1 subject (3%; 75 mg). All events resolved without intervention. In the Phase 2 study in patients with ADHD (N = 41), there were no potential abuse-related TEAEs reported.
Conclusions: The data from the preclinical studies suggest that while CTN has DA activity, it does not induce stimulant-like behaviors in animals. In humans there were no TEAEs that would reflect a concern or signal for abuse liability at therapeutic doses that may provide efficacy in ADHD; a few potential abuse-related TEAEs were observed at the maximum evaluated dose, but these were also accompanied by aversive effects. This early stage assessment may suggest a lower potential for abuse for CTN compared to stimulants. However, because of its (intended) ability to increase DA, a clinical abuse liability study is in progress to further evaluate the abuse potential of 2 doses of CTN relative to d-amphetamine, lisdexamfetamine dimesylate and placebo in recreational stimulant users.
Keywords: Centanafadine, Abuse Liability, ADHD.
Disclosure: Brigitte Robertson; Employee of Neurovance, Megan J. Shram; Employee of Altreos, Kerri A. Schoedel; Employee of Altreos, Tim Hsu; Employee of Neurovance, Catherine, Obrien; Employee of Neurovance, Frank P. Bymaster; Employee of Neurovance.

W161. Trait and State Functional Connectivity Disruptions in Default and Salience Networks in Those with Active and Remitted Major Depressive Disorder

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Background: We previously used functional connectivity MRI (fcMRI) to examine low frequency oscillations in brain networks among young adults in the remitted state of Major Depressive Disorder (rMDD). Individuals with rMDD demonstrated hyperconnectivity of the default mode network (DMN) and salience network (SN) with regions of the cognitive control network (CCN). These findings suggest that some hyperconnectivities may represent traits that can be observed outside of episode, rather than states associated with acute illness. Few studies have examined connectivity in both the remitted (rMDD) and active (aMDD) phases of MDD to parse the nuances of state and trait effects that may be related to compensatory mechanisms or risk for relapse. The current sample of unmedicated, young adults towards the end of cognitive maturation is hypothesized to bear less of a lifelong cumulative burden of illness. We hypothesized that hyperconnectivities between key nodes of the DMN and the SN with the CCN would be evidence of trait risks for MDD and would be present in both rMDD and aMDD participants compared to Healthy Controls (HCs).
Methods: fcMRI data were acquired over eight minutes in 3.0 Tesla scanners across two sites: the University of Michigan and the University of Illinois at Chicago. As movement is an area of particular concern for fcMRI studies, we first evaluated average standard deviations of movement in the x, y, and z planes in a sample of 34 Healthy Controls (HCs), 38 rMDDs, and 32 aMDDs. Two methods

were used to reduce the influence of movement on results: 1) normality plots of the average standard deviation of movement values in the x, y, and z plans were examined and those with values greater than 2 standard deviations were excluded, 2) individuals with any TR to TR movements greater than .5mm across three consecutive TRs were excluded. These exclusion criteria resulted in a final sample of 34 young adults with between 1 – 3 prior episodes of MDD (using the Diagnostic Interview for Genetic Studies; DIGS) who had been remitted for at least one month and had a HAM-D score ≤ 7). Twenty six healthy control (HC) individuals had usable data and no personal or family history of mood disorders. Seventeen individuals in the aMDD group were assessed with structured diagnostic interviews prior to entering clinical trials. All participants were medication free for at least two weeks prior to scanning. Across groups the average age was 21.4 (SD = 1.6) and 65% of the sample was female. Participants rested with eyes open while viewing a fixation crosshair to elicit coherence of resting state networks. Data were processed and analyzed using MATLAB and SPM8, including slice timing, realignment, coregistration, warping, and smoothing with a 5 mm FWHM. The left posterior cingulate cortex (PCC, -5, -50, 36), left subgenual anterior cingulate cortex (sgACC, -4, 21, -8), and left amygdala (-23, 5 -19) were used as seeds to analyze connectivity within and between the DMN and SN. Three-dimensional correlation coefficient images were transformed to z scores and z images were used to conduct two-sample t-tests. AlphaSim was used with 1000 Monte Carlo simulations to determine whole brain correction with a joint threshold of height and extent ($p < .005$, cluster extent of 440 mm3) for group comparisons.

Results: For the PCC seed, a significant effect of group was detected in the inferior frontal ($F = 4.13$) and medial frontal ($F = 3.77$) gyri as well as the cingulate ($F = 4.46$). The finding in the IFG derived from the rMDD group demonstrating greater connectivity than the aMDD group ($z = 4.3$), whereas the aMDD group demonstrated hyperconnectivity between the PCC and cingulate ($z = 4.85$) when compared to the rMDD group. Hyperconnectivity between the PCC and the medial frontal gyrus (MFG) was observed in aMDD compared to rMDD participants ($z = 3.29$). Using the sgACC seed, a significant effect of group was detected in the orbital frontal gyrus ($F = 4.06$) and the hippocampus ($F = 4.01$) and derived from hyperconnectivity among the rMDD group compared to the aMDD group. For the amygdala seed, a significant group effect deriving from hyperconnectivity to the claustrum was detected across the aMDD + rMDD (all MDD) compared to HCs.

Conclusions: This is the first study to examine resting state connectivity during the active and remitted states of MDD among a late-adolescent sample. We found that individuals in the remitted state demonstrated hyperconnectivity between the DMN and CCN when compared to those in the active state. Greater connections between the CCN and DMN may allow individuals greater control over self-referential thought, contributing to or reflective of remission. Individuals in the remitted state also demonstrated increased connectivity between SN nodes with more effortful (sgACC) and automatic (hippocampus) emotion regulation regions when compared to individuals suffering from acute depression. Among those in an acute episode, greater connectivity between the amygdala and insula (claustrum) was observed compared to those in remission from MDD. Collectively, these findings suggest that hyperconnectivities are related to both state and trait features of depression. Ongoing clinical follow-up will allow for testing of whether these patterns predict relapse or resilience.

Keywords: depression, fMRI, connectivity, state.
Disclosure: Nothing to Disclose.

W162. New Repeat Polymorphism in the (AKT1) Gene Predicts Striatal D2/D3 Receptor Availability and Stimulant Induced Dopamine Increases in Human Brain

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Background: The protein kinase Akt1regulates a cascade of intracellular molecular events initiated by DRD2- and DRD3 receptor stimulation that is known as the non-canonical signalling pathway. Variations in the AKT1 gene might therefore influence dopaminergic (DA) signaling in the human brain. Indeed, previous studies have examined an association of several AKT1 SNPs with conditions of disrupted DA activity, including psychiatric disorders (schizophrenia and addiction) and age. The information value of specific markers within the AKT1 locus remains unclear, and the influence of AKT1 genetic variations on baseline DA circuitry and sensitivity to DA enhancing drugs is largely unknown. Here we report a newly identified repeat polymorphism in the AKT1 gene (VNTR). We explored its impact on DRD2/D3 receptors availability at baseline and on the dopamine increases induced by Methylphenidate (MP) in healthy individuals. For this purpose we scanned participants with PET with 11C raclopride twice: first – after placebo and second – after MP administration.

Methods: 79 individuals of Caucasian descent were originally recruited to participate in different PET imaging studies at BNL Imaging Center as healthy controls and also agreed to provide a genetic sample for the analysis. Genotyping was performed by PCR using in house flanking primers and optimized conditions of amplification. Individual genotypes were ascribed based on the amplicon lengths (high-H and low-L), and participants were assigned to either one of three genotype groups (LL, HL and HH). Under unknown genetic model, we used three-genotypes classification. 11C raclopride images were used to assess the effect of the AKT1 genotype on raclopride's non-displaceable binding potential (BPND) at striatal regions at baseline and following MP administration (0.5 mg/kg, i.v). MP-induced increases in DA were measures as the changes in BPND between placebo and MP. Images were analyzed using ROI-based (SPSS) - and voxel-based (SPM) approaches.

Results: In the study population the frequencies of the two VNTR alleles were similar at about 50%. SPSS analysis (GLM) indicated that the availability of DRD2/D3 receptors in heterozygote carriers of VNTR allele (HL) was significantly higher than in homozygotes (caudate: $F(2,75) = 5.8$,

$p < 0.01$ and thalamus: $F(2,75) = 4.76$, $p = 0.01$). We observed an interaction between the genotype and age on DRD2/D3 receptor availability across striatal sub-regions (caudate: $F(3,75) = 15.3$, $p < 0.001$; putamen: $F(3,75) = 5.9$, $p = 0.001$ and thalamus: $F(3,75) = 4.7$, $p = 0.004$). The results from SPM-based analysis corroborated those findings, revealing that LL-genotype group had significantly lower DRD2/D3 availability (peak in right putamen: pFWE corr = 0.005; T65 = 3.49) and steeper slope of age-associated decline in striatal DRD2/D3 availability (pFWE corr. = 0.012, T = 3.14). The AKT1 VNTR differentially affected the magnitude of MP-induced DA increase (assessed as changes in striatal BPND between placebo and MP): relatively modest decrease in BPND following MP administration observed in the LL-group (peak in right putamen: pFWE corr = 0.01; T112 = 4.09) which contrasted with the pronounced changes in the HL- and HH-groups (peak in right putamen: pFWE corr < 0.0001; T112 = 99.25 and pFWE corr < 0.0001; T112 = 160, respectively). The differences in MP response between the genotype groups were statistically significant with a peak in right putamen: (BPND delta in HL > LL: pFWE corr < 0.039; T56 = 2.32 and HL > HH: pFWE corr < 0.021; T94 = 2.63).

Conclusions: Our results are in line with the previous clinical and epidemiological findings associating the human AKT1 gene with brain DA circuitry, highlighting an informative value of new VNTR in this locus as a potential marker for future imaging genetic studies of higher brain functions and drug addiction.

Keywords: AKT1 gene, striatum, dopamine, PET.

Disclosure: Nothing to Disclose.

W163. Clinical Characteristics of Children with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) Phenotype

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Background: Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) is a subtype of acute-onset obsessive compulsive disorder (OCD) marked by an abrupt onset or exacerbation of neuropsychiatric symptoms (e.g., reduced and restricted food intake, sensory symptoms, handwriting deterioration, separation anxiety, and/or emotional lability). The immune-driven hypothesis for PANS proposes that antibodies produced in response to an infection cross the blood-brain barrier and interfere with neuronal signaling, causing a manifestation of neuropsychiatric symptoms. The current treatment for youth meeting PANS criteria include immune therapies, prophylactic antibiotic therapy, and the same standard of care practices for pediatric OCD (i.e., psychopharmacological and/or behavioral treatment). We aim to characterize PANS by phenotypic analysis of study participants.

Methods: Characteristics (e.g., OCD severity, presence of infectious trigger) of 43 children ages 4 to 14 years who met criteria for PANS were assessed using self-report and clinician administered measures, medical record reviews, comprehensive clinical evaluation, and laboratory measures. Measures for symptom severity included the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) for OCD, the Yale Global Tic Severity Scale (YGTSS) for tics, the Child-Global Assessment Scale (C-GAS) for overall functioning, and the parent-rated Child Health Questionnaire Parent Form 50 (CHQ-PF50) for quality of life.

Results: Youth presented with an early age of OCD onset (mean = 7.84 years ± 2.65) and exhibited moderate to severe obsessive-compulsive symptoms (CY-BOCS Total Score mean = 28.3 ± 5.0) upon evaluation. All had comorbid anxiety and emotional lability, with separation anxiety (77%) reported as the most common type, followed by generalized anxiety (47%) and school avoidance (47%). The majority of youth also presented with mild motor and/or vocal tics (n = 30; YGTSS Total Tic Severity Score mean = 15.5 ± 7.81). Overall, PANS youth displayed large deficits of quality of life. Specifically, parent report of Mental Health (Well-Being) on the CHQ-PF50 (Mean = 47.18) was far below the national average (Mean = 78.50), indicating a higher frequency of anxiety and depressive symptoms in this sample. Most youth (n = 30, 75%) scored between 41 through 60 on the C-GAS, indicating moderate social impairment in most areas or severe impairment in one area, and 20% (n = 8) of participants scored 40 or below, indicating major impairment or inability to function. Nearly one-third of participants reported suicidal ideation or self-injurious behaviors. Analyses of group differences revealed several significant findings. First, youth with tics presented more frequently with IgA deficiency, decline in school performance, food refusal symptoms, handwriting deterioration, and lower quality of life compared to youth without tics. Second, males were identified as having more frequent presentations of anti-DNAse B titer elevations and endorsement of sexual/religious obsessions. Third, youth with elevated streptococcal antibody titers had significantly higher OCD severity and presented more frequently with dilated pupils. A cluster analysis of core PANS symptoms revealed three distinct symptom clusters, including: (1) core characteristic PANS symptoms (e.g. emotional lability, anxiety, behavioral regression); (2) strep-related symptoms (e.g., streptococcal titers, urinary symptoms); and (3) cytokine-driven physiological symptoms (e.g., food restriction, mydriasis, fatigue). Approximately half of youth presented with two or more symptoms in this cluster (51%), with 76% of all youth endorsing at least one symptom in this cluster.

Conclusions: The sudden, acute-onset of neuropsychiatric symptoms, high frequency of comorbidities (i.e. anxiety, behavioral regression, depression, and suicidality), and poor quality of life define the PANS subgroup as a suddenly and severely impaired group of youth. Identifying clinical characteristics of these youth will allow clinicians to diagnose and treat this subtype of OCD with a more strategized and effective approach. The distinction between PANS-related and non-PANS OCD is of particular importance as youth with PANS often have severely impairing symptoms, and may respond to psychiatric medications and/or therapy differently than youth with classic presentations of OCD.

Keywords: Pediatric Acute-Onset Neuropsychiatric Syndrome, Obsessive compulsive disorder, Neuroimmunology, Tic Disorders.

Disclosure: This work was supported by a grant from the Massachusetts General Hospital.

W164. An Empirical Test of the Definition of MDE Recovery

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Background: We analyzed the validity of two levels of major depressive episode (MDE) recovery included in the current consensus definition of recovery: 8 consecutive weeks totally free of all symptoms of the preceding MDE (asymptomatic recovery) vs. 8 consecutive weeks with mild residual subsyndromal depressive symptoms (SSD resolution). The primary test of the validity of the two definitions is duration of the first well interval.
Methods: The NIMH Collaborative Depression Study (CDS) is a longitudinal follow-up investigation of the prospective, naturalistic course of unipolar and bipolar disorders. 322 subjects entering the CDS in a unipolar MDE were divided at recovery into 2 groups: those with 8 consecutive weeks with no symptoms of the intake MDE, and those with 8 consecutive weeks with mild residual depressive symptoms. Level of intake MDE recovery, time to the first depressive episode, and long-term depressive illness burden were based on weekly Psychiatric Status Ratings (PSRs) of symptom severity on all depressive conditions. The primary measure of the validity of the two definitions was duration of the first well interval, determined by survival analysis. Groups were also compared on depressive illness burden during 10, 15, and 20 years after the start of asymptomatic vs. SSD intake MDE recovery. The recovery groups were also compared on clinical history, intake episode characteristics, comorbidity, antidepressant medication treatment, and psychosocial impairment.
Results: 61.2% of subjects met the definition of asymptomatic recovery, while 37.8% had SSD resolution of their intake MDE. Median time well for asymptomatic recovers was 2.5 times longer to MDE relapse/recurrence, and 4.2 times longer to the next depressive episode of any type. This was not attributable to differences in level of antidepressant medication treatment during either the intake episode or the first well interval. Asymptomatic recoverers also had a significantly lower depressive illness burden over the next 10, 15, or 20 years. SSD resolution of the intake MDE was associated with significantly longer and more severe intake MDEs, more irritability and miscellaneous psychopathology at intake, and greater pre-morbid psychosocial impairment. However, level of recovery from the intake MDE was a more significant predictor of time to relapse/recurrence than any of 16 other clinical predictors examined.
Conclusions: It is now becoming widely recognized that the goals of MDE treatment are amelioration of acute symptoms of the episode, establishment of a stable state of recovery, restoration of the individual's pre-morbid level of psychosocial function, and reduction of future course chronicity. The present study provides strong evidence that only asymptomatic recovery meets all of these treatment goals and should be considered 'true' MDE recovery. Results add to the growing literature showing that MDE resolution to the level of subsyndromal residual depressive symptoms does not constitute true recovery; further, combining this under the rubric of 'asymptomatic' recovery, as is often done in the literature, is inaccurate and misleading. Retention of residual depressive symptoms indicates that the episode is still active, with the patient continuing to have significant psychosocial impairment and high risk for rapid relapse/recurrence.
Keywords: Major Depression, Recovery Definition, Asymptomatic Status, Residual Symptoms.
Disclosure: Nothing to Disclose.

W165. The Path Toward Making Psilocybin Available for Medical Use: New Findings and Analyses Related to Abuse Potential and Safety

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Background: Psilocybin has been used and studied for more than one-half century as a treatment for various mental disorders including anxiety, depression, and substance dependence in the United States and several other countries. Since its regulation as a schedule I (CI) controlled substance under the 1970 United States Controlled Substances Act (CSA), however, there have been severe constraints on its use in research. In brief, schedule I is the CSA placement for drugs that (a) have a high potential for abuse, (b) are not approved by the Food and Drug Administration (FDA) for medical use, and (c) have not been found acceptably safe for use under medical supervision. Clinical research and other research since the 1990s suggests that psilocybin has important medicinal benefits, can be safely administered, and is characterized by a relatively low abuse and physical dependence potential profile compared to schedule II and III opioids, stimulants, and depressants. The potential indication under recent study is severe anxiety/depression secondary to cancer diagnosis in patients who are refractory to standard care options. The therapeutic approach would likely involve no more than two doses to be administered in controlled settings by specially trained staff. This poster will summarize clinical and nonclinical studies relevant to abuse potential evaluation according to the CSA 8 factor assessment tool, including new data and analyses. The poster will also present an evaluation of original data from several completed studies, and preliminary results from ongoing studies that are relevant to evaluation of safety.
Methods: Several Phase I and Phase II studies were conducted and are ongoing, including administration of psilocybin at various dose levels to healthy volunteers to evaluate the pharmacodynamics and efficacy in several potential therapeutic applications in people with various psychiatric disorders. Adverse event data across studies were coded using metrics similar to those used in safety and efficacy clinical trials for other CNS drugs. All of the clinical studies were conducted under Investigational New Drug applications and with Institutional Review Board approval at academic medical centers. Doses ranged from 14 mg/70 kg to 30 mg/70 kg, given at intervals of at least one week, usually twice, and never more than three times per volunteer. The test session rooms were supportive therapeutic settings. Trained counselors monitored events, recorded data, and offered reassurance. Several of the

studies included double-blind comparisons to placebo and one study included 40 mg/70 mg methylphenidate as a comparator drug. More than 200 volunteers have been exposed to at least one, and more typically to two or three doses of psilocybin in the Heffter Research Institute collaborative studies. Safety data evaluations are ongoing and data from many/most of these exposures will be presented.

Results: Results that have been collected (and in some cases presented or published at the time this abstract was developed) included the following: (1) Psilocybin at all doses was generally well tolerated, resulting in no serious adverse events requiring emergency interventions, (2) Psilocybin did not produce effects that were readily characterized as either sedating or stimulating but rather induced a unique profile of effects characterized by perceptual changes (e.g. visual illusions), labile mood (e.g. feelings of transcendence, grief, joy, and/or anxiety), and cognitive changes (e.g. a sense of meaning or insight). (3) Follow-up evaluations at one to 14 months revealed lasting effects, with psilocybin sessions generally described in positive terms as among the most meaningful events of the person's lifetime, with resulting increases in spirituality and quality of life indicating improvements that were persistent; (4) initial findings in cancer patients suggest reductions in anxiety and depression symptoms. A preliminary evaluation of the eight factors of the CSA for the purpose of developing a drug scheduling recommendation included analysis of chemistry, pharmacology, preclinical data, epidemiology, and other clinical evidence. The analysis supports a plausible recommendation for CSA regulation as a schedule IV drug.

Conclusions: Taken together, these findings suggest potential therapeutic efficacy for symptoms of anxiety and depression secondary to cancer diagnosis in patients refractory to standard care. Medical risks and side-effects were generally mild and manageable by study staff. The evidence does not suggest a high risk of abuse or dependence. A potential application for approval would include a Risk Evaluation and Mitigation Strategy (REMS) that would likely restrict distribution directly to the health care providers (HCPs), limit dosing, require certification that HCPs had been appropriately trained, and would include appropriate evaluation and follow-up of all patients.

Keywords: Psilocybin, Safety, Abuse Potential.

Disclosure: Nothing to Disclose.

W166. Altered Anxiety Expression in Anorexia Nervosa: Effects of an Interoceptive Pharmacological Challenge with Isoproterenol

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Background: Prior to food avoidance and weight loss, individuals with anorexia nervosa (AN) routinely exhibit increased threat sensitivity, hypervigilance and pervasive avoidance. This suggests that anxiety sensitivity may represent an intermediate phenotype of eating disorders. Although anxiety disorders are well known clinical antecedents to AN and other eating disorders, remarkably little is known about how anxiety-related interoceptive sensations are subjectively experienced in real time by persons with AN. With respect to panic anxiety, interoceptive sensations of a pounding heartbeat and difficulty breathing are the most commonly reported symptoms. In the current study we assessed the experience of anxiety and panic in individuals with anorexia nervosa across a wide range of arousal levels using infusions of isoproterenol, a peripheral beta adrenergic agonist, to induce these sensations. We hypothesized that individuals with AN would display greater levels of anxiety than matched healthy comparisons during interoceptive stimulation with isoproterenol and saline. We also predicted that individuals with AN would exhibit greater levels of panic than healthy comparisons.

Methods: We assessed anxiety and panic experience using a randomized, double-blinded, and placebo controlled design, in 15 individuals with AN and 15 age- and sex- matched healthy comparisons (HC). Participants rated the experience of anxiety and panic immediately following multiple bolus infusions of isoproterenol and saline, during two conditions: 1) panic provocation and 2) meal consumption. During the panic provocation condition participants completed a DSM 5 panic symptom rating scale following each of 7 bolus intravenous infusions, administered in a single blinded, fixed order (0.1 mcg, saline, 4 mcg, saline, 1 mcg, 2 mcg, saline). A classification system based on DSM criteria was used to define whether subjects experienced a panic attack. During the meal condition participants completed the same rating scale after receiving 14 bolus intravenous infusions, double blinded, in random order: 7 isoproterenol (0.1, 0.25, 0.5, 0.75, 1, 2, 4 mcg) and 7 saline, before and after eating a 1000 Calorie meal. Continuous variables were analyzed using repeated measures GLMs and independent t-tests. Dichotomous variables were analyzed using the Chi square test.

Results: Bolus isoproterenol infusions elicited equivalent increases in heart rate in both groups across the panic and meal conditions ($p < .0001$). There were no significant group differences or group by condition interactions (all p's $> .05$). There were also no group differences in adrenergic sensitivity as measured by CD25 (dose required to elevate the heart rate by 25 beats per minute; $t(28) = -.99$, $p = .34$). As expected, both groups endorsed increased anxiety at increasing doses the panic and meal conditions (all p's $< .0001$). Consistent with predictions, prior to the panic and meal conditions the AN group reported greater anticipatory anxiety than HCs ($F(1,28) = 6.4$, $p = .018$). The AN group also exhibited higher anxiety than HCs before and after meal consumption ($F(1,28) = 7.8$, $p = .009$), but only at a trend level during the panic provocation condition ($F(1,28) = 3.3$, $p = .08$). After adjusting for responses to saline there were no longer any group differences in the magnitude of anxiety increase, across all conditions (all p's $> .05$). As predicted, we found that a significantly greater proportion of the AN group panicked during the pre meal condition $\chi 2(1) = 3.96$, $p = .046$), but found no significant post meal differences. Surprisingly, there were no differences in panic rates during the panic provocation condition ($p > 0.05$).

Conclusions: Consistent with predictions, we found that individuals with AN exhibit higher anxiety levels and panic

more frequently than healthy comparisons during induction of interoceptive sensations. However, they experience the same magnitude of change in anxiety as healthy comparisons in response to induction of interoceptive sensations. These results suggest that elevated apprehension of interoceptive sensations may be an underlying phenotype contributing to AN, and that pre-meal periods signify distinct foci of fear inherent to this illness. Specific interventions aiming to habituate meal associated anxiety may represent a targeted and useful treatment approach.
Keywords: Anorexia nervosa, anxiety, interoception, panic.
Disclosure: Nothing to Disclose.

W167. Rates of Non-publication of Trials Funded by the Stanley Medical Research Institute

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Background: Progress in developing drugs in medicine in general and in psychiatry in particular is played by non-publication of studies. We examined rates of publication of 253 studies funded by the Stanley Medical Research Institute (SMRI) since the year 2000.
Methods: We reviewed all studies funded by SMRI from 2000 to 2009 (N = 253).
Results: Of these studies, 12.3% were not completed. Of the studies completed, rates of publication ranged from 73% of those funded in 2000 to 26% of those funded in 2006. Mean rates of publication from 2000 to 2009 was 46.3%. Mean time to publication ranged from 1 to 4 years. Further analyses will be done in order to compare the primary outcome measures which are indicated in these studies' protocols and the outcomes presented in the publications.
Conclusions: Rates of publication in SMRI are similar to those of studies in non-psychiatric fields funded by the NIH. Lack of communication of results is damaging for the field, as compounds which have already been tested but have not been published might be tested again, leading to unnecessary exposure of patients to study procedure/placebo and to a waste of funds that might be used for innovative compounds instead. Thus, funding agencies might consider holding part of the grant's payment until the study's results are published.
Keywords: Publications, psychiatry, clinical trials.
Disclosure: Nothing to Disclose.

W168. Association of Body Mass Index with Anatomical Architecture of Reward Network Regions in Healthy Subjects

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Background: Similarities between brain mechanisms involved in maladaptive obesity-related ingestive behaviors and addictive behaviors have resulted in the concept of food addiction. Structural (gray matter), anatomical (white matter), and functional (evoked or resting state) alterations in key brain regions of an extended reward network have been linked to increased ingestive behaviors in obesity. With recent advances in more efficient and computationally intense mathematical algorithms, it has become possible to characterize the architecture of regions in large-scale networks in specific disorders. The most fundamental network measure is degree or the connectedness of a particular region to other regions. Regions with high degree are considered essential for maintaining global connectedness. Another measure is the clustering coefficient, which reflects the fraction of a region's neighbors that are also neighbors with each other and are thought to be key nodes for clusters or modules in the brain. High clustering efficiency is associated with greater efficiency in transferring information between regions. We hypothesized that BMI is associated with differences in degree and clustering coefficients of key regions comprising the extended reward circuit.
Methods: White and grey matter was measured in 99 healthy, male and female subjects who completed structural and diffusion tensor imaging (DTI) MRI scans. Data processing workflows were created using the USC Laboratory of Neuroimaging (LONI) Pipeline. Regional parcellation was conducted using Freesurfer based on the Destrieux and Harvard Oxford atlases, and resulted in 74 bilateral cortical and 7 subcortical structures, including the cerebellum. Relative fiber density between regions was obtained using deterministic tractography and the Runge-Kutta algorithm. Anatomical network metrics were generated using the Brain Connectivity Toolbox and were constructed from the threshholded correlation matrix between the 165 cortical and subcortical regions. Controlling for the main effects of age and sex, the general linear model was applied to examine the association between BMI with degree and clustering coefficients of regions comprising the extended reward network. The regions investigated included thalamus, amygdala, insula, prefrontal and orbitofrontal cortices, anterior cingulate cortex and nucleus accumbens/ventral striatum. We also include an interaction term to determine whether the interaction between ETI and topology of the regions of interest were moderated by sex. Significance was set at $p < .05$ uncorrected.
Results: 1. Subject Characteristics: There were 57 lean individuals (mean BMI = 22.08kg/m2, sd = 1.54, range = 18.19-24.4kg/m2) and 42 non-lean individuals (mean BMI = 29kg/m2, sd = 3.85, range = 25.0-43.6kg/m2). No significant age differences were observed between the lean group and the high BMI group. 2. Association between BMI and degree of reward regions. After controlling for age and sex, BMI was positively associated with degree of left thalamus ($\beta = 1.14$, $p = .04$), left caudate ($\beta = .67$, $p = .04$), and right nucleus accumbens ($\beta = .83$, $p = .03$). On the other hand BMI was also negatively associated with degree of the right ventromedial prefrontal cortex ($\beta = -.62$, $p = .03$). 3. Association between BMI and local clustering coefficient efficiency of extended reward regions: After controlling for age and sex, BMI was significantly positively associated with local efficiency for the right amygdala ($\beta = .009$, $p = .02$) and left nucleus accumbens ($\beta = .008$, $p = .04$). On the other hand, BMI was also negatively associated with local efficiency of the right anterior insula ($\beta = -.006$, $p = .01$),

bilateral ventromedial prefrontal cortex ($\beta = -.005$, $p = .03$; $\beta = -.007$, $p = 05$). Interaction effects were not observed for sex and BMI on degree or clustering coefficient measures.
Conclusions: The anatomical network architecture of regions within the reward network are associated with BMI. Findings indicate that higher BMI is associated with more local and regional communication between regions often associated with increased dopamine production, and less information propagation was observed in the cognitive frontal regions. Longitudinal studies will be required to address the question of causality between BMI and network alterations and the association with ingestive behavioral patterns. Compared to regional activity or grey matter measures, anatomical network properties may serve as more sensitive central biomarkers and possibly predictors of outcome for obesity treatments.
Keywords: obesity, network metrics, reward network, anatomical connectivity.
Disclosure: Supported by NIH grants P30 DK041301, R01 DK048351, P50DK64539. UCLA Ahmanson-Lovelace Brain Mapping Center (Pilot Scanning).

W169. Maternal Prepubertal Adversity Predicts Gestational Age at Delivery, Infant Birthweight, and Infant Head Circumference

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Background: Prepubertal adversity can have lasting impact on the maternal hypothalamic-pituitary-adrenal (HPA) axis, which may subsequently influence the fetal HPA axis and birth outcomes. As part of a longitudinal study examining the effect of maternal HPA axis dysregulation on the fetal and infant HPA axes, we investigated the effects of maternal prepubertal adversity and prenatal psychosocial stress on gestational age at delivery, infant birthweight, and infant head circumference.
Methods: 146 pregnant women 8-17 weeks gestation were recruited from University of Pennsylvania OB/GYN practices. Eligible participants were $\geq$ 18 years with no active psychiatric diagnosis, no serious medical illness, and no history of preterm birth. Participants completed the Adverse Childhood Experience Questionnaire (ACE) and the Perceived Stress Scale (PSS). Their obstetric and infant records were examined for important maternal and neonatal outcomes. Data regarding gestational age at delivery, infant birthweight, and infant head circumference for women with ACE scores of 0 or 2 + are presented here. Univariable linear regressions were used to identify how maternal prepubertal adversity and prenatal psychosocial stress were associated with gestational age at delivery, infant birthweight, and infant head circumference. Multivariable linear regressions were performed to account for maternal race/ethnicity, socioeconomic status, parity history, and pregnancy complications in describing the associations among ACE scores, PSS scores, and delivery outcomes. Maternal substance abuse was not included as the number of women who abused substances during pregnancy was too small.
Results: Of the 146 enrolled women, 58.2% had a prepubertal ACE score of 0, 24% had a prepubertal ACE score of 1, and 17.8% had a prepubertal ACE score of 2 or more. Prepubertal ACE score was positively correlated with PSS score ($r = .24$, $p = .01$) In univariable regression analyses, maternal prepubertal ACE score of 2 + was significantly associated with earlier gestational age at delivery ($p = .04$) but not smaller head circumference ($p = .19$). There was a trend towards an association with lower infant birthweight ($p = .08$). Greater prenatal psychosocial stress was significantly associated with earlier gestational age at delivery ($p = .02$) and lower infant birthweight ($p = .004$). There was a trend towards an association with smaller infant head circumference ($p = .07$). In multivariable regression analyses, maternal prepubertal ACE score of 2 + was significantly associated with lower birthweight ($p < .001$) but not gestational age at delivery ($p = .26$). There was a trend towards an association with smaller infant head circumference ($p = .08$). Greater prenatal psychosocial stress was not associated with lower birthweight ($p = .58$) or smaller head circumference ($p = .39$), although there was a trend towards an association with earlier gestational age at delivery ($p = .07$).
Conclusions: Maternal prepubertal adversity is a significant predictor of poor delivery outcomes, even after adjusting for key maternal variables. Maternal prepubertal adversity may have effects on delivery outcomes that are more influential than the effects of prenatal psychosocial stress.
Keywords: Trauma, Pregnancy, Birth Outcomes, Women's Mental Health.
Disclosure: Deborah Kim.

W170. Does the Level of Education Relate to Severity of Suicidality as Measured by the Sheehan-Suicidality Tracking Scale (S-STS)? An Analysis with an Adult Psychiatric Inpatient Population

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Background: The topic of education and suicide is minimally addressed in the empirical literature. Theoretically, this relationship was first proposed by Durkheim (1951), who argued that higher education inhibits social cohesion. His report emphasized the role of social cohesion and community integration in preventing suicide. The existing research on education and suicide remains inconsistent and carries methodological limitations. Mortality data from the United States (Lester, 1985) and Italy (Pompili et al., 2013) have revealed associations between higher educational attainment and suicide rates. A study of Danish first-time psychiatric inpatients revealed that postgraduate education was associated with an increased suicide risk post-discharge (Agerbo, 2007). This post-hoc analysis aims to expand the existing research on education and suicidality and specifically focus on psychiatric patients. This exploratory-based analysis is significant for several different reasons. As described earlier, the empirical research is scarce on education and suicide, in general. Furthermore, the relationship between education and suicide has been minimally studied with a psychiatric

population. Second, there are methodological concerns for the existing research reporting suicide rates. The existing research, which is based on national databases, may be affected by underreporting. Furthermore, methodological limitations surrounding ambiguous terminology and unclear definition have caused conflict with suicide research (Meyer et al., 2010).
Methods: Adult psychiatric inpatients (N = 199) completed standardized suicide assessment interviews as part of the original psychometric study. A self-report demographic questionnaire collected highest level of education. The severity of suicidal ideation and behavior was measured by using the Sheehan-Suicidality Tracking Scale (S-STS), a standardized suicide assessment (Coric et al., 2009). In the current study, the S-STS was delivered in either an interview or self-report format. S-STS subscale scores for past-month suicidal ideation and behavior served as the outcome variables for this analysis.
Results: Multiple linear regression analyses were conducted in order to test for predictive relationships between highest level of education and scores on the S-STS ideation and behavior subscale scores. Highest level of education ($\beta = 0.12$, $t(196) = 1.74$, $p = 0.08$) just missed significance at predicting suicidal ideation after controlling for gender. Highest level of education ($p = 0.48$), was not a significant predictor of suicidal behavior after controlling for gender.
Conclusions: Although a higher level of education predicted an increased score on the suicidal ideation subscale of the S-STS, this relationship just missed significance. There was no evidence for a predictive relationship between the level of education and score on the suicidal behavior subscale of the S-STS. If Durkheim was correct in his assessment that higher education inhibits social cohesion, it is perhaps the case that psychiatric inpatients were already significantly marginalized and any effect of education could have been masked. Additional variables such as race or ethnicity may also further explain the relationship; for example, Stack (2000) found that the direction of the relationship between the risk of death by suicide and level of educational attainment varied between African-American and Caucasian men. Future studies should continue to address this underserved topic, particularly among psychiatric inpatients who are at a high risk of suicide.
Keywords: Suicide, Suicide Assessment.
Disclosure: Alan J. Gelenberg has the following to disclose: Zynx Health (consultant), Healthcare Technology Systems, Inc. (stock shareholder). The original psychometric evaluation study was supported by an investigator-initiated award from Pfizer, Inc. to Penn State Hershey Medical Center (PI: Alan J. Gelenberg).

W171. The Role of Early Life Stress in Suicidality Among Treatment-seeking Alcohol Dependent Inpatients

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Background: Both suicide and alcohol dependence (AD) are significant public health problems. Suicide is the tenth leading cause of death among adults in the United States, and the third leading cause of death among U.S. adolescents. The annual prevalence rates for alcohol use disorders are approximately seven percent for adults in the U.S.; alcohol-related problems cost over $200 billion dollars each year. The relationship between suicide and AD is complex. In general, alcohol consumption positively correlates with rates of suicide. Further, individuals with alcohol use disorders report higher rates of suicidal ideation and attempts than the general population. In addition, alcohol consumption is a significant risk factor for completed suicides. Among those individuals who commit suicide, data suggests that a substantial proportion have consumed alcohol just prior to death. Thus, understanding the relationship between these two phenomena is essential for alleviating the enormous public health burdens presented by both suicide and AD. Although the mechanisms linking suicide and AD are unclear, one potential candidate is early life stress (ELS). ELS comprises various experiences, and includes traumatic events such as physical, emotional, and sexual abuse, and neglect. ELS is a known risk factor for later development of AD. Among individuals with AD, higher trauma load is positively associated with increased severity of addiction and risk for psychiatric comorbidity. In addition, trauma increases the risk for both suicidal ideation and attempts. Childhood sexual abuse (CSA) is one particular form of ELS that specifically increases risk for AD as well as for suicide. The rate of exposure to CSA varies, with estimates ranging from 10 to 30% in females and 5 to 15% in males. The aim of the present study is to examine the effects of CSA on suicidal ideation and attempts among a sample of treatment-seeking inpatients diagnosed with AD.
Methods: Subjects included 442 treatment-seeking individuals undergoing inpatient detoxification and treatment at the National Institute on Alcohol Abuse and Alcoholism clinical treatment research unit at the National Institutes of Health Clinical Center in Bethesda, MD. Individuals were diagnosed with AD according to the Structured Clinical Interview for DSM-IV and stayed at NIH for approximately four weeks. Exposure to ELS was measured using the Childhood Trauma Questionnaire, which assesses five subtypes of maltreatment, including CSA. Alcohol dependence severity was measured using the Alcohol Dependence Scale (ADS), and lifetime suicidal ideation and attempts were assessed using the Addiction Severity Index. The average age of subjects was 43 years; 67% of the sample was male, and half were Caucasian. Approximately 26% of subjects had considered, while 14% had attempted suicide. The average CSA score on the CTQ was 7.46 (SD: 5.49), in the mild range. Data were analyzed using logistic regression, with the presence or absence of suicidal ideation or attempts as the primary outcome variables. Independent variables included CSA exposure, alcohol dependence severity, gender, age, years of education, and lifetime history of Major Depressive Disorder (MDD).
Results: Data analysis indicated that CSA, gender, ADS score, and MDD all significantly predicted lifetime suicidal ideation. Odds ratios (OR) were as follows: CSA, 1.054 (95% CI: 1.053-1.054), $p = 0.018$, female gender, 1.848 (95% CI: 1.842-1.854), $p = 0.023$, ADS score, 1.053 (95% CI: 1.053-1.053), $p = 0.001$, and MDD lifetime diagnosis, 2.010 (95%

CI: 2.014-2.017), p = 0.011. The OR for CSA indicates an approximately five percent increase in risk of suicidal ideation for each one unit increase on the CTQ. For lifetime suicide attempts, significant predictors included CSA, female gender, and MDD. Odds ratios (OR) were as follows: CSA, 1.076 (95% CI: 1.075-1.076), p = 0.003, female gender, 2.790 (95% CI: 2.779-2.802), p = 0.003, and MDD lifetime diagnosis, 2.371 (95% CI: 2.361-2.380), p = 0.011. The OR for CSA indicates an approximately eight percent increase in risk for suicide attempts for each one point increase on the CTQ.

Conclusions: Results indicated that exposure to CSA, gender, dependence severity, and lifetime history of MDD, were all significant predictors of suicidality among treatment-seeking alcoholics. It is important to note that it is the severity of CSA, not its presence or absence, which was associated with increased risk for suicidal ideation and attempts in our sample. These findings suggest a complex relationship between CSA and later sequelae, such as psychiatric disorders and gender. Of note, additional analyses including posttraumatic stress disorder (PTSD) diagnosis as an independent variable did not find it to be a significant predictor of suicidality in our sample. Further, there was no significant interaction between exposure to CSA and gender, which suggests that these two factors may operate somewhat independently from each other, at least in this sample. Future directions for the present research include exploring behavioral phenotypes of AD, including suicide, and conducting a mediation analysis to understand how these various factors may interact with each other.

Keywords: Alcohol dependence, Suicide, Trauma, Early life stress.

Disclosure: Nothing to Disclose.

W172. Olfaction is Associated with Ability to Recognize Emotions in High Functioning Autistic Subjects

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Background: Olfaction is important for social interactions in animals. In autism, altered olfaction may contribute to abnormal processing of socially salient information and provide a biomarker indexing disruptions of the embryogenic development within critical time-frames. We assessed olfaction in high-functioning adults with autism and its relation to auditory and visual emotion recognition.

Methods: 19 High-functioning adults (M = 23.4 years, FSIQ = 99.95 SD = 14) with autism participated in a cross-over placebo-controlled pharmacological intervention study. Data obtained in the placebo session was used. Olfaction identification was evaluated with the "Sniffin' Sticks" test; emotion recognition with the Affective Speech Recognition (ASR) and the Reading-Emotions-in-the Eye (RMET) tests; functioning with the Vineland Adaptive Behavior Scale. Patients were grouped into normal (normosmic N = 10) and impaired (hyposmic N = 7; anosmic N = 2) olfactory identification groups based on normative data by the publisher of the test (score of 9 or less).

Results: Patients with impaired olfaction showed significantly worse performance in the ASR overall (46% ± 0.02 [SE] correct versus 67% ± 0.02 [SE] correct) and across all emotions presented (anger, disgust, fear, happiness, lust, sadness, surprise) compared to normoosmic subjects. They performed worse on the RMET (42% vs 57% correct). Smell correlated modestly with the composite and communication scores on the VABS (r = 0.42; r = 0.49), the FSIQ (r = 0.43) and VIQ (r = 0.45).

Conclusions: Olfaction is considered the most ancient of all the human senses, with links to brain areas responsible for cognitive, visceral, emotional, and homeostatic behaviors. In humans, olfactory cues may contribute conspecific recognition and communication. Impaired olfaction may contribute to more deficient development of social communication in autism and/or index more severe pathology in brain circuits subserving social communication. Olfactory capabilities may serve as a biomarker easily assessed clinically, providing information on the state of a phylogenetically important system for social communication and useful for stratification in clinical trials.

Keywords: Autism Spectrum Disorder, Emotion recognition, Olfaction, Biomarker.

Disclosure: D. Umbricht, M. del Valle Rubido, O. Khwaja, L. Squassante, L. Boak and P. Fontoura are employees of F. Hoffmann - La Roche, Ltd.

W173. 3D Modeling of the Dorsal Prefrontal White Matter Pathways Involved in Psychiatric Disorders

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Background: The dorsal prefrontal cortex (DPFC) is a large prefrontal region (areas 8, 9, 10 and 46) plays a major rule in top-down control, executive functions, regulation of emotional drive and risk taking behaviors, working memory, and planning (Fuster, 2008). The DPFC connects with anterior and posterior cingulate cortices, superior temporal cortex, premotor regions, and orbitfrontal cortex (Barbas and Pandya; 1989), as well as the lateral and medial parietal cortex and a number of subcortical areas, including the dorsal striatum (Petrides and Pandya, 1999). DPFC dysfunction is associated with psychiatric disorders, such as depression (Mayberg 1997), obsessive compulsive disorder (Nakao et al., 2005), schizophrenia (callicott et al., 2000; Zhou et al., 2007) and addiction (Goldstien and Volkow, 2011). Neuroimaging studies demonstrate volume and microstructure abnormalities in psychiatric disorders in different white matter (WM) pathways connecting the DPFC with other cortical and subcortical regions. For instance, studies show abnormality in dorsal anterior limb of internal capsule (ALIC), the genu of the corpus callosum (CC) and superior longitudinal fasciculus (SLF) in schizophrenia (Skudlarski et al 2013). Other studies demonstrate abnormality in the posterior body of CC, external capsule (EC) and fornix, ventral ALIC and uncinate fasciculus (UF) in depression (Jia et al., 2010). In OCD, studies found abnormality in central ALIC, cingulum bundle (CB) and anterior body of CC (Togaoet al., 2010). Other studies found WM abnormality in the genu and body of CC, CB, ALIC and

EC in addiction (Lin et al., 2012). The aim of this study is to delineate and compare the trajectories of fibers from the different DPFC regions, and their positions within the major PFC pathways. This will give us a better understanding of the relation between WM specific pathways and abnormalities in the DPFC reported by the imaging research of psychiatric disorders.
Methods: We used immunocytochemistry and computerized 3D modeling to illustrate the efferent pathways from different location in the DPFC of nonhuman primates. We placed 23 injections of anterograde/bidirectional tracers into macaque DPFC, then charted the axon pathways, beginning from the injection site. These charts were combined into a 3D rendering in order to compare fiber trajectories across cases.
Results: Fibers from different injection sites enter and travel in the WM and split into different major pathways: The ALIC, EC, the CB, the CC, Muratoff's Bundle (MB) and the SLF. Fibers from dorsomedial regions (area 9m/8B) also travel in the fronto-occipital fasciculus (FOF). Fibers from more dorsal regions,(area 9D, 46D) use the medial longitudinal fasciculus (MLF) and the fornix, extreme capsule. Fibers from more lateral injection (area 46v) use UF but not the dorsal fiber bundles in addition to the major bundles. Thus, axons from a specific region consistently split to new pathways traveling to different destinations. Importantly, in some of the major fiber bundles, such as the CC and ALIC, fibers from different DPFC regions occupy distinct territories positions within the fiber bundle. These axons adhere to a topographic organization, based on their caudal-rostral/medial-lateral and dorsal-ventral position in the DPFC. From these bundles, fibers from different regions in the DPFC travel to unique cortical and subcortical destinations.
Conclusions: Psychopathology imaging literature describes various pathway abnormalities related to the different psychiatric disorders. In this study we traced the different DPFC pathways from their origin to their destinations. We found that the position of fibers in DPFC determines which route and position those fibers occupy through the bundle in their trajectory and determines their destination. In addition, based on analysis of our results and converging diffusion imaging data of psychiatric disorders we were able to link specific bundles and specific DPFC regions with the different mental disorders pathology.
Keywords: pathways, Schizophrenia, mood disorders, addiction.
Disclosure: Nothing to Disclose.

W174. Distress Intolerance is Associated with Prescription Opioid Misuse in Chronic Pain Patients

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Background: Prescription opioid abuse has reached an epidemic level in the US, with higher rates of unintentional overdose than heroin and cocaine combined. Although the majority of individuals with chronic pain who are prescribed long-term opioid therapy are able to adhere to prescribed medication regimens, a large portion of patients (30-50%) will exhibit misuse or abuse of their medication. Despite the growing prevalence of opioid abuse, relatively little is known about predictors of this problem in chronic pain populations. The current study examines differences between those with and without opioid abuse on a hypothesized affective vulnerability factor: distress intolerance. Distress intolerance, the perceived inability to tolerate negative physical and emotional states, is an important risk and maintaining factor in substance use disorders that is associated with levels of use, motivation for use, presence of substance use disorders, and treatment outcome. Distress intolerance is a powerful motivator of harmful avoidance behaviors (e.g., substance use) that provide strong and immediate relief from distressing states. For someone who is highly intolerant of distress, behaviors that provide rapid relief become relied upon to regulate distress in the absence of alternative strategies. In chronic pain, the inability to tolerate pain and emotional responses to pain (e.g., anger, anxiety) may lead to the abuse of opioids to attempt to avoid these sensations.
Methods: A sample of patients with chronic back or neck pain receiving treatment in a pain management clinic who were prescribed opioids ($N = 39$, 46% female) were recruited for this study. The average age of participants was 55 years ($SD = 7.9$) and the majority of the sample self-reported race as Caucasian (74%). Participants completed self-report and behavioral measures of distress intolerance, a battery of pain reactivity tests, and measures of opioid abuse.
Results: Results from a linear regression with level of opioid abuse as the dependent variable found that distress intolerance was a strong predictor of opioid abuse ($t = 4.67$, $p < .001$; $R2 = .61$), even when controlling for age, gender, and severity of pain ($t = 4.60$, $p < .001$; $R2 = .62$). Participants meeting the clinical cut-off on the Current Opioid Misuse Measure had a mean distress intolerance score almost twice that of those below the cut-off ($t = -4.45$, $p < .001$).
Conclusions: Distress intolerance was strongly associated with prescription opioid abuse in a sample of chronic pain patients. Thus, distress intolerance may be an important treatment target for those with chronic pain taking opioid medications. Important directions for future research will include the testing of DI interventions for reducing opioid abuse and longitudinal analyses of this association to determine whether DI predicts opioid abuse among opioid-naive pain patients.
Keywords: Prescription drug abuse, Opioids, Distress intolerance, Chronic pain.
Disclosure: Nothing to Disclose.

W175. Non-steroidal Anti-inflammatory Treatment Reduces the Effects of Early Life Stress on Depressive-like Behavior in Adolescent Females

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Background: The emergence of sex differences in depressive illness occurs during adolescence, a time when females are

more sensitive to stress and exhibit a higher rate of depression than males. Chronic early life stress increases the risk for the development of depression during this period. A potential underlying mechanism for the onset of depression following early life stress may be increased neuroinflammation. Our previous studies found that male rats that were separated from their mother and littermates before weaning (maternal separation; MS) had increased expression of cyclooxygenase-2 (COX-2), a key player in the inflammatory pathway. We have also shown that juvenile treatment with a COX-2 inhibitor prevents working memory deficits following MS in male rats. In this study, we examined the effects of COX-2 inhibition on motivational deficits associated with depressive-like behavior following MS in female rats. We also investigated whether an acute stress exposure (i.e. witnessing their peers receive shocks) exacerbated these effects and their intervention with COX-2 inhibition.

Methods: Female Sprague-Dawley rat pups (n = 7-8/group) were maternally separated for four hours/day and kept at a thermoneutral temperature or animal facility reared (CON) between postnatal days (P) 2 and P20. On P21, pups were weaned and group-housed (3-4/cage) until experimentation. Females were then treated with a COX-2 inhibitor (NS-398, 8 mg/kg, i.p.) or vehicle (Veh; DMSO) every other day between P30 and P38. On P40, motivational deficits associated with depressive-like behavior were examined using the no shock (NS) condition of the learned helplessness triad. More specifically, on Day 1 of LH, NS rats either witnessed (WIT; an acute stress exposure) a rat that underwent 100 trials of an escapable tail shock in a wheel-turn box or were only gently restrained in the testing apparatus in a separate room. On Day 2, all females were placed into a shuttle box for 30 trials. Subjects were able to terminate a 1-mA foot shock by shuttling to the other side for trials 1–5, or by shuttling to the other side and back again for trials 6–30. This response was cued by a tone that preceded the shock by 2 s. The shock remained on for 30 s, or until terminated by the appropriate behavioral response. The number of escape failures and the mean latency to escape the shock was measured.

Results: In a 2(early life stress) x 2(treatment) x 2(WIT) ANOVA, an interaction between MS and WIT ($F1, 50 = 5.41$, $P = 0.02$) and a main effect of treatment ($F1, 50 = 5.89$, $P = 0.02$) overall for average escape latency. A 3 way interaction between stress x treatment x WIT was observed for the number of escape failures ($F1, 50 = 4.49$, $P = 0.04$). To better understand how the acute stress exposure affected treatment effects, subsequent analyses were divided into two separate groups. When examining the effects of MS in the no WIT group, a stress x treatment interaction was observed on the latency to escape ($P = 0.047$) and on the number of escape failures ($P = 0.03$). Latency to escape the shock was increased in MS Veh females when compared to CON Veh. COX-2 treatment decreased the latency to escape in MS but not CON females, suggesting that this treatment is effective only in animals with a stress history. To test this, animals with a shorter stress exposure (WIT) had an overall treatment effect ($P = 0.02$) where COX-2 decreased escape latency of both MS and CON females. It is important to note that the CON WIT females took longer to escape when compared to MS WIT females.

Conclusions: Our studies show that early intervention with a non-steroidal anti-inflammatory treatment can prevent the behavioral consequences of stress in adolescent females. Recent studies have suggested that witnessing a traumatic event can have long lasting effects on behavior. Our findings demonstrate that hearing another peer get shocked induces motivational deficits associated with depressive-like behavior that are reduced by prior COX-2 exposure. However, without an acute stress exposure COX-2 treatment was only effective in MS females. Our data suggest a history of stress, regardless of length of exposure, is necessary for COX-2 treatment to be effective. These studies increase our understanding of the mechanisms through which neuroinflammation and adverse experiences may interact to increase risk for depression in females, and identify novel targets in vulnerable individuals during a sensitive period of development for not only intervention, but also the prevention of depression.

Keywords: maternal separation, female, depression, neuroinflammation.

Disclosure: Nothing to Disclose.

W176. Alterations of Mitochondrial DNA Copy Number and Telomere Length with Early Adversity and Psychopathology

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Background: Telomere shortening and alterations of mitochondrial biogenesis are involved in cellular aging. Childhood adversity is associated with telomere shortening, and several investigations have shown short telomeres in psychiatric disorders. Recent studies have examined whether mitochondria might be involved in neuropsychiatric conditions, but findings are very limited and no prior work has examined this in relation to stress exposure.

Methods: Two-hundred and ninety healthy adults provided information on childhood parental loss and maltreatment and completed diagnostic interviews. Participants were categorized into four groups based upon the presence or absence of childhood adversity and the presence or absence of lifetime psychopathology (depressive, anxiety, and substance use disorders). Telomere length and mtDNA copy number were measured from leukocyte DNA by qPCR.

Results: Childhood adversity and lifetime psychopathology were each associated with shorter telomeres ($p < .001$) and higher mtDNA copy numbers ($p < .001$). Significantly higher mtDNA copy numbers and shorter telomeres were seen in individuals with major depression, depressive disorders, and anxiety disorders, as well as those with parental loss and childhood maltreatment. A history of substance disorders was also associated with significantly higher mtDNA copy numbers.

Conclusions: This study provides the first evidence of an alteration of mitochondrial biogenesis with early life stress and with depressive, anxiety, and substance use disorders. We replicate prior work on telomere length and psycho-

pathology, and show that this effect is not secondary to medication use or comorbid medical illness. Finally, we show that early life stress and psychopathology are independently associated with these markers of cellular aging.
Keywords: mitochondria, telomere, stress, depression.
Disclosure: Nothing to Disclose.

W177. The Expression of Developmentally-regulated PGC-1alpha-Dependent Genes is Reduced in the Cortex of Patients with Schizophrenia

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Background: PGC-1alpha (peroxisome proliferator-activated receptor-gamma coactivator 1-alpha) is a transcriptional coactivator expressed in tissues with high metabolic demand. Several reports have linked PGC-1alpha to psychiatric disorders including anxiety disorder, bipolar disorder, and schizophrenia, but its involvement in the pathophysiology of these disorders is unclear. Previous experiments utilizing whole body and neuron-specific PGC-1alpha knockout mice revealed a set of cortical PGC-1alpha-dependent transcripts involved in calcium buffering (parvalbumin – PV), synchronous neurotransmitter release (synaptotagmin 2 – Syt2; complexin 1 – Cplx1) and axonal integrity (neurofilament heavy chain – Nefh). To determine whether PGC-1alpha function is altered in schizophrenia, we measured these four PGC-1alpha-responsive genes in the anterior cortex of patients with schizophrenia. To investigate the functional implications of these findings, we explored the temporal regulation of these transcripts during brain development and their cell-specific localization in human brain.
Methods: Quantitative RT-PCR was used to measure the expression of PGC-1alpha, PV, Syt2, Cplx1, and Nefh in the anterior cortex of patients with schizophrenia (Stanley set, $n = 33$/group), and confocal and immunoelectron microscopy were used to localize PGC-1alpha-dependent genes to different cell types.
Results: We found that the expression of all four PGC-1alpha-dependent genes was reduced in the anterior cingulate of patients with schizophrenia, a change which could not be recapitulated in rats treated chronically with the antipsychotic drug haloperidol. While control subjects with high PGC-1alpha expression exhibited high PV and Nefh expression, patients with schizophrenia did not, suggesting a disrupted association between the expression of PGC-1alpha and its targets in schizophrenia. In fact, in the same samples, we found a reduction in the expression of nuclear respiratory factor 1 (Nrf1), a PGC-1alpha-interacting transcription factor with multiple putative binding sites in the proximal promoters of PV, Syt2, Cplx1, and Nefh. We then evaluated the expression profile of these transcripts throughout normal human cortical development ($n = 269$); all transcripts increased significantly between birth and early adulthood in normal postmortem human cortex samples. Immunoreactivity for Syt2, Cplx1, and Nefh overlapped with PV in the cell bodies and processes of cortical interneurons, and Syt2 and Nefh were also found in excitatory neurons and synapses.
Conclusions: These data suggest that schizophrenia involves a disruption in a PGC-1alpha-associated developmental transcriptional program in multiple cortical cell types and that approaches to enhance PGC-1alpha activity or the activity of associated transcriptional regulators could restore normal maturation-related gene programs and potentially improve cortical function. These data will be discussed in the context of mouse studies currently ongoing in the Cowell lab to determine the physiological and behavioral impact of PGC-1alpha deletion in PV-positive neurons and pyramidal neurons.
Keywords: transcription, interneuron, parvalbumin, postmortem.
Disclosure: Nothing to Disclose.

W178. Novel Antiepileptic Carisbamate Alters the Subjective Effects of Alcohol in Human Subjects

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Background: Topiramate has been shown to reduce heavy drinking days in patients with alcohol-use disorder (AUD). Both carisbamate and topiramate decrease alcohol self-administration in rodents. Carisbamate shares a similar method of action with topiramate but is significantly more tolerable with fewer side effects (somnolence, dizziness, cognitive disturbances) and does not require rapid titration. Proposed method of action of carisbamate is by blunting glutamatergic transmission and facilitating the inhibitory action of GABA. Carisbamate was previously tested as a treatment for epilepsy and was shown to be well tolerated.
Methods: Participants were screened using DSM IV TR criteria for alcohol dependence. Upon determination that participants had Alcohol Use Disorder (AUD), they were admitted to the Research Commons and randomized to placebo vs. carisbamate twice daily (at 8 am and noon). On day 4, participants received a mildly intoxicating dose of alcohol and a matched placebo (0.8 g/kg) 2 hours after each carisbamate dosing. Subjective effects of alcohol were monitored using the Drug Effects Questionnaire (DEQ), the Positive and Negative Affect Schedule (PANAS), Alcohol Urge Questionnaire (AUQ), and Biphasic Alcohol Effects Scale (BAES). Alterations in mood were monitored with a daily Beck Depression Inventory (BDI). Participants were monitored via breath alcohol content and systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) every 15 minutes. Two weeks later participants received the alternative medication (carisbamate vs placebo) and procedures were repeated. Using a two-way (placebo/carisbamate) repeated measures (Time) ANOVA for analysis, paired t-test for baseline SBP.

Results: No main effects for treatment (placebo vs. carisbamate) for subjective measures, however there were main effects for Time for LIKE ($p < 0.001$) and WANT ($p = 0.005$) and a trend for HIGH ($p = 0.089$). There was a trend for a treatment effect for BAC ($p = 0.064$) and SBP ($p = 0.099$) a significant main effect for TIME for BAC, SBP and DBP ($p < 0.001$) and a trend for HR ($p = 0.086$). Baseline SBP significantly differed between treatment groups ($p < 0.001$). No significant adverse events were noted.
Conclusions: Carisbamate did not significantly alter the subjective effects of alcohol. Carisbamate did however tend to increase BAC. Treatment with carisbamate was associated with lower baseline SBP compared to placebo. Carisbamate tended to enhance the effects of alcohol but the effect did not reach statistical significance, likely due to sample size.
Keywords: Alcohol Dependence, Carisbamate, Substance Related Disorders.
Disclosure: Nothing to Disclose.

W179. The Antidepressant Effects of GLYX-13 Are Mediated by Medial Prefrontal Cortex-associated Long Term Potentiation-like Synaptic Plasticity

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Background: GLYX-13 is an N-methyl-D-aspartate receptor (NMDAR) functional partial agonist that is safe and shows antidepressant activity in both rodent models and humans. GLYX-13 has been shown to: a) preferentially enhance conductance of NR2B-containing NMDARs at rat Schaffer collateral-CA1 synapses in vitro; b) enhance the magnitude of long-term potentiation (LTP) of synaptic transmission, while simultaneously reducing that of long-term depression (LTD). GLYX-13 has also been shown to: a) enhance performance in several hippocampus-dependent learning tasks in both young adult and learning-impaired aged rats; and b) produces antidepressant-like effects in a variety of animal models without ketamine-like dissociative, addictive or sedative side effects. To study the mechanisms underlying these effects, we used a 21-day chronic unpredictable stress (CUS) rat model. We evaluated the effects of CUS alone compared to No CUS controls, and the effects of GLYX-13 on CUS-treated animals.
Methods: Chronic Unpredictable Stress (CUS) Procedure: Male Sprague-Dawley rats (2-3 Months old) received 21 days of CUS: (9 different CUS stressors, 2 stressors per day). Animals in the CUS groups received a single optimal dose of GLYX-13 (3 mg/kg iv; $n = 10$) previously shown to produce a robust antidepressant-like response or sterile saline vehicle ($n = 10$). Porsolt Test: Animals were placed in a 46 cm tall x 20 cm in diameter clear glass tube filled to 30 cm with tap water (23 ± 1 °C) for 15 min on the first day (habituation) and 5 min on the subsequent test days (1 hr, 24 hrs, 1 week, 2 weeks post-dosing). Sucrose Preference Test: Rats were exposed to a palatable 1% sucrose solution for 48 hours, followed by 4 hours of water deprivation and a 1 hour exposure to two identical bottles, one filled with sucrose solution and the other with tap water. Novelty Induced Hypophagia (NIH) Test: Animals were food deprived on the night before testing, and lab chow was placed into the center chamber of the open field (40 x 40 x20 cm) for 10 min under dim-red lighting. Positive Emotional Learning (PEL) Test: Animals received 3 min of heterospecific rough-and-tumble play and frequency modulated 50-kHz ultrasonic vocalizations were measured during a conditioned stimulus that predicts play. Contextual Fear Conditioning (CFL) Test: Animals received three 0.5 mA, 1 sec footshocks delivered to the floor bars of a 40 X 40 X 40 cm shock chamber during the acquisition day. During extinction, rats received 5 min non-reinforced test trial every 24 hr for 6 consecutive days, and on day 14 post-conditioning (consolidation trial). Microarray Analyses: Triplicate microarray analyses were performed using the medial prefrontal cortex (MPFC) isolated from individual CUS treated animals injected with GLYX- 13, vehicle, or no CUS control rats. Medial Prefrontal Cortex Slice Electrophysiology: In vitro slices were prepared from CUS-treated rats 24 hours after a single injection of GLYX-13, vehicle, or no CUS control rats. Normalized field EPSP slopes evoked in layer II/III and recorded in layer IV of rat MPFC were measured before and after application of high-frequency theta burst stimulation used to induce LTP.
Results: CUS produced a depressive-like effect in Porsolt, sucrose preference, and novelty-induced hypophagia tests, as well as impaired medial prefrontal cortex (MPFC) dependent positive emotional learning (PEL) and contextual fear extinction (CFE). GLYX-13 administered to CUS-treated rats produced a complete reversal of the depressive-like state in each of the depression models, and the reversal of learning and memory deficits seen in both the PEL and CFE models. The ability to induce LTP in the MPFC was markedly suppressed in CUS-treated rats, and GLYX-13 restored LTP in CUS animals to control levels. Transcriptomic analysis of MPFC mRNA expression corroborated the link between GLYX-13 and synaptic plasticity processes. We observed a marked enrichment in both the LTP and LTD connectomes in GLYX-13-treated CUS rats, compared to no-drug CUS-treated rats.
Conclusions: Traditional NMDAR antagonists, such as ketamine, lead indirectly to enhanced glutamate release, resulting in the modulation of synaptic plasticity and antidepressant effects. Our data with GLYX-13 suggest a new mechanism for glutamatergic-based antidepressant effects via direct activation of MPFC-localized NMDARs that persistently lowers the threshold for induction of LTP.
Keywords: NMDA Receptor, Depression, Medial Prefrontal Cortex, Long Term Potentiation.
Disclosure: Joseph Moskal, Roger Kroes, Amanda Gross, Mary Schmidt, and Ronald Burch are employees of Naurex, Inc. Jeffrey Burgdorf, John Disterhoft, J. David Leander, and Patric Stanton are consultants for Naurex, Inc. Xiao-lei Zhang and Craig Weiss receive salary support from a grant from Naurex, Inc., to Patric Stanton and John Disterhoft respectively. Over the last 3 years J. David Leander has received financial compensation and/or stock with the following companies: AgeneBio, Nektar, and CoLucid.

W180. The Interaction of Food Intake and Voluntary Alcohol Intake: Effects of Incentive Motivation and Devaluation

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Background: Several lines of research support the interaction of food intake and nutritional systems in alcohol abuse and dependence. Alcohol, a calorically rich food as well as a drug of abuse, is consumed excessively after food deprivation and moderate alcohol administrations can increases food consumption. We report that rats deprived of food before initial alcohol exposure had greater chronic alcohol consumption than that of those non-deprived before initial alcohol access. Attempts to devaluation the ethanol (EtOH) reinforcement by giving free access to alcohol before testing failed to alter the increased preference of animals exposed to EtOH when hungry.
Methods: Male Sprague-Dawley rats were divided into two groups: food deprived (23 hrs) or ad lib. fed rats. All rats given initial access to 3% EtOH in water for 1 hr. Experimental rats were then deprived of food for 23 hr prior to 1 hr EtOH access. These animal were given the same amount of 3% EtOH that ad lib. controls consumed during the previous session. This pair-feeding paradigm was to control for the effects of the amount of EtOH exposure prior to testing. Animals were given 3 sessions separated by 3 days of ad lib. food and water between food deprivation paired with EtOH intake sessions. All animals consumed the same quantity of alcohol during the three 1 hour sessions prior to two bottle choice testing. EtOH concentrations increased from 1 to 10% during this testing. After the completion of testing, selected high drinking rats of both EtOH and control groups were given ad lib. access to EtOH for three days and then tested again in the two bottle choice. This procedure was to explore the effects of devaluation of the EtOH reinforcement observed in the previous testing.
Results: The initial experiences with alcohol in a food deprived state produced greater EtOH consumption during the two–bottle choice testing. Animal in this group consumed more alcohol than those that experience with alcohol under ad lib food consumption. Ad lib access to EtOH (devaluation) effects on two-bottle choice produced a slight reduction in alcohol intake; however, the greater consumption of the food-deprived animals remained during this devaluation.
Conclusions: These data indicate that there is indeed an important effect of food deprivation with alcohol intake. The effect is not simply due to the calories and other reinforcing effects of alcohol, but also to the increased incentive value of alcohol when consumption occurs during the high drive state of food deprivation. Animals that first experienced alcohol under the hunger state consumed more alcohol that those first experiencing alcohol under ad lib conditions. The effect was not due to greater alcohol consumption of the food deprived animals during the intial exposure period, since the amount of EtOH consumed was the same for both groups. The effects of devaluation of alcohol reinforcement by ad lib. consumption only partially suppressed alcohol consumption and was less potent in animals that experienced alcohol under food deprivation. The interaction of food intake mechanisms with the motivation to drink alcohol is complex involving several reinforcement mechanism. These may play a significant role in alcohol abuse and dependence.
Keywords: Alcohol intake, Food deprivation, incentive motivation, Devaluation.
Disclosure: Nothing to Disclose.

W181. Ketamine and the mGlu2/3 Receptor Antagonist LY341495 Rapidly Engage Dopaminergic Mood Circuits to Engender Antidepressant-related Behavioral Effects

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Background: Ketamine is a rapidly-acting antidepressant in treatment-resistant depressed patients with effects that can last for several days. The mechanisms of action underlying these effects are not fully established, but likely involve the release of glutamate as the initiator of a biological cascade. A large body of preclinical data suggests that blockade of mGlu2/3 receptors would also have antidepressant effects. The ability of mGlu2/3 receptor antagonists to increase synaptic glutamate levels further suggests the possibility that mGlu2/3 receptor antagonists might trigger other core mechanisms of action that are similar to those of ketamine. The brain's dopamine systems are recognized as end-targets for mood regulation and hedonic valuation.
Methods: We examined the actions of ketamine and the mGlu2/3 receptor antagonist LY341495 on electrophysiological, neurochemical, and behavioral measures of the dopamine system in rats.
Results: When given acutely, both ketamine and LY341495, but not the selective serotonin uptake inhibitor (SSRI) citalopram, increased the number of spontaneously active dopamine neurons in the ventral tegmental area (VTA), increased the synaptic availability of dopamine in the nucleus accumbens and prefrontal cortex, and enhanced the locomotor stimulatory effects of the dopamine D2/3 agonist quinpirole. Further, both ketamine and LY341495 reduced immobility time in the tail-suspension assay in mice (CD1) that are resistant to SSRI antidepressants.
Conclusions: These findings indicate that the rapid engagement of dopamine neurotransmission may play an important role in the remarkable clinical pharmacology of ketamine and other potential rapidly-acting antidepressants, including mGlu2/3 antagonists.
Keywords: ketamine, LY341495, mGlu 2/3.
Disclosure: The authors are employees and stockholders of Eli Lilly & Co.

W182. A Novel Function for Matrix Metalloproteinases in Animal Models of Mood Disorders and Schizophrenia

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Background: Matrix metalloproteinases (MMP's) are a family of protease enzymes that degrade extracellular

matrix proteins and process bioactive molecules. Of these, MMP-9 is one of the most abundant in the CNS and is involved in synaptic plasticity, LTP, modulation of network connectivity, and modulation of NMDAR and synaptic activity through cleavage of proteins such as reelin, integrin, and b-dystroglycan. MMP-9 activity is induced during events that require plasticity and remodeling, by cytokines or excitotoxicity, and an overabundance of MMP-9 activity can promote demyelination, blood brain barrier disruption, cell death, oxidative stress, and inflammation. These functions of MMP-9 in the CNS suggest that it could be involved in the long-term regulation of processes or proteins related to mood disorders or schizophrenia. The aim of this study was to determine the effects of a potent MMP-9 inhibitor, Compound A, in animal models of mood disorders and schizophrenia.

Methods: Compound A was tested on the prevention of learned helpless (LH) induced escape and female urine sniffing deficits in rats. Mice were injected with lipopolysaccharide (LPS, 0.6 mg/kg), to induce inflammation, or vehicle, and tested in tail suspension test (TST) the next day. Compound A or vehicle was injected with LPS and 15 min before TST. Plasma was collected after TST for an angiogenesis panel and frontal cortex (2 h post-LPS in a separate cohort) for microarray. Compound A was tested on amphetamine (2.5mg/kg) disruption of prepulse inhibition (PPI) in rats. Compound A was tested on naloxone (10mg/kg) conditioned place aversion (CPA) with morphine given ~18 h before each conditioning. Hyperactivity was recorded after morphine and escape jumps during the last conditioning. Compound A was injected before each conditioning and after each morphine.

Results: In the in LH model, Compound A prevented the development of anhedonic- and despair-like state. In the inflammatory depression model, Compound A decreased immobility time in TST and attenuated several transcriptional responses to LPS. Preliminary data suggest that Compound A may blunt the LPS-induced increases in several cytokines. In a schizophrenia model, Compound A partially reversed amphetamine-disruption of PPI. In a model of bipolar disorder, Compound A was shown to attenuate morphine hyperactivity and naloxone-induced dysphoria, as measured by CPA and escape jumping.

Conclusions: The data suggest that Compound A exerts its antidepressant-like, antipsychotic-like, and mood-stabilizing effects in animal models through its anti-inflammatory or neuroprotective actions, or by attenuating aberrant CNS plasticity induced by negatively impacting events. Hence, MMP-9 inhibition may put the break on constant, ongoing remodeling of the diseased brain. These data highlight MMP-9 inhibitors as a novel class of possible therapeutic targets.

Keywords: depression, bipolar, schizophrenia, animal models.

Disclosure: The authors were employed by Janssen Research & Development, LLC at time of research.

W183. Lurasidone Treatment Regulates Clock Gene Expression in the Chronic Mild Stress Model

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Background: An important element of mood disorders is the disruptions in circadian rhythms. This has led to hypothesize that abnormalities in the molecular clock may contribute to the development of these disorders and that normalization of these changes may be important for therapeutic efficacy. The cellular clock is a transcriptional-translational feedback loop involving a number of different genes that may possess separate functions in circadian rhythms and mood regulation. While this machinery has been extensively characterized in the suprachiasmatic nucleus, little is know on the role exerted by individual clock genes in other brain structures important for mood disturbances, such as hippocampus and prefrontal cortex, where circadian rhythmicity of gene expression has also been observed. In the present study we have employed the chronic mild stress (CMS) model of depression to establish changes in the expression of the clock gene machinery in different brain regions as a consequence of stress exposure and we also investigated the properties of the multi-receptor modulator lurasidone to regulate such alterations.

Methods: Male Wistar rats were exposed to CMS for 2 weeks and sucrose consumption was used to identify rats that were susceptible to the stressful manipulation. Control and CMS-susceptible rats were then randomized to receive chronic vehicle or the multi-receptor modulator lurasidone (3 mg/kg/day) for 5 more weeks, while continuing the stress procedure, in order to evaluate the ability of chronic drug treatment to normalize the behavioral and molecular phenotype associated with CMS. Real time PCR was used to investigate the expression of clock genes including Clock/Bmal1, Per1 and Per2, Cry1 and Cry2.

Results: We found that the mRNA levels for Per1 and Per2 were significantly down-regulated in the prefrontal cortex of CMS rats, an effect that was associated with a slight up-regulation of Bmal1 expression. No changes were found for Clock mRNA levels, whereas a significant stress-induced reduction was also found for Cry2 (but not Cry1) expression. Interestingly, chronic treatment with lurasidone, was able to normalize the anhedonic phenotype as well as the molecular changes produced by stress exposure. The modifications of Per1 and Per2 expression after exposure to CMS appear to be anatomically selective, since we did observe similar changes in dorsal or ventral hippocampus as well as in the hypothalamus. However, chronic treatment with lurasidone was able to up-regulate some of these genes in hippocampal sub-regions, the largest changes occurring on Cry1, Per1 and Per2.

Conclusions: We believe that changes in clock gene expression as a consequence of CMS exposure may contribute to the disturbances associated with mood disorders and may bridge circadian abnormalities with neuronal function in critical brain regions. With this respect, the ability of chronic lurasidone to modulate clock gene expression in association with its ability to normalize the anhedonic phenotype in CMS rats provide further support to its therapeutic properties in ameliorating

functions that are deteriorated in patients with major depression and stress-related disorders.
Keywords: stress, gene expression, clock, prefrontal cortex.
Disclosure: This project was supported by funding from Sunovion/Sumitomo Dainippon Pharma Co.

W184. Effects of Pharmacological and Environmental Manipulations on Methamphetamine vs. Food Choice in Rhesus Monkeys

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Background: Methamphetamine (METH) addiction is a significant public health problem for which there are no Food and Drug Administration-approved pharmacotherapies. Preclinical choice procedures provide a simplified model of behavioral allocation between an alternative non-drug reinforcer and intravenous METH injections. Furthermore, a choice procedure was utilized because a major goal of treating METH addiction is not only to decrease METH-taking behavior, but also to increase behavior maintained by alternative, non-drug reinforcers. Moreover, preclinical choice procedures have demonstrated predictive validity of pharmacological treatments in both human laboratory and clinical trial settings for the abused drugs cocaine and heroin. However, there are no published studies examining either pharmacological or environmental manipulations on METH reinforcement using a preclinical choice procedure. We hypothesized that METH will maintain a dose-dependent increase in choice over an alternative, non-drug reinforcer (food pellets). Furthermore, we hypothesized pharmacological manipulations (bupropion and risperidone) that have been examined in clinical trials would show similar effects in our METH vs. food choice procedure in nonhuman primates.
Methods: Adult, male rhesus monkeys (n = 3-4) were surgically implanted with a chronic indwelling, double-lumen venous catheter and trained to self-administer METH under a concurrent schedule of food delivery (1-gram pellets, fixed-ratio 100 schedule) and METH injections (0.01 – 0.32 mg/kg/injection, fixed-ratio 10 schedule). Daily choice sessions were implemented from 0900 – 1100 and consisted of five 20-min components, with a different unit METH dose available during each successive component (0, 0.01, 0.032, 0.1, and 0.32 mg/kg/injection during components 1-5, respectively). One lumen of the double-lumen catheter was designated as the "METH" lumen and was always filled with the self-administered METH solution. The other lumen was designated as the "treatment" lumen, and saline, the monoamine uptake inhibitor and nicotinic acetylcholine receptor antagonist bupropion (0.32 – 1.8 mg/kg/h) or the dopamine antagonist risperidone (0.001 – 0.0056 mg/kg/h) was continuously infused 23 hs/day during 7-day treatment blocks. Treatment blocks with bupropion or risperidone were counter-balanced both within a test compound dose and across test compounds. For comparison to these pharmacological manipulations, the effects of removing the food or METH reinforcer for 7-days on methamphetamine vs. food choice was also determined.
Results: Under saline treatment conditions, food was primarily chosen during availability of low unit METH doses (0.01 – 0.032 mg/kg/injection), choice was approximately 50% when 0.1 mg/kg/injection METH was available, and METH was primarily chosen only during availability of the highest unit METH dose (0.32 mg/kg/injection) examined. Rates of operant responding decreased as a function of increasing unit METH doses. Removing food pellet availability during the choice session significantly increased responding on the METH-associated key during availability of 0.032 and 0.1 mg/kg/injection unit METH doses and resulted in greater METH intake. In contrast, substituting saline for METH resulted in a significant decrease in responding on the previous METH-associated key and a reciprocal increase in responding on the food-associated key. Continuous bupropion treatment failed to significantly alter METH vs. food choice up to doses that significantly decreased rates of operant responding. Continuous risperidone treatment produced a dose-dependent increase in METH vs. food choice. The highest dose of risperidone also significantly decreased rates of operant responding.
Conclusions: Methamphetamine was chosen over an alternative non-drug reinforcer allowing for the assessment of pharmacological mechanisms that mediate METH reinforcement. Consistent with previous clinical trials, continuous bupropion and risperidone treatment failed to produce the desired behavioral profile of decreasing METH choice and producing a reciprocal increase in food choice. Overall, these preclinical results using a METH vs. food choice procedure provide an empirical foundation for the development of novel candidate medications in treating methamphetamine addiction.
Keywords: Methamphetamine, Bupropion, Addiction, Medication Development.
Disclosure: This research was funded by National Institutes of Health Award Numbers R01DA031718 and R01DA012970.

W185. Role of Serotonergic Transmission in Antidepressant Effects of an mGlu2/3 Receptor Antagonist and Ketamine

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Background: Abnormalities in glutamatergic systems have been implicated in pathophysiology of depression, and targeting glutamatergic system may be an effective approach to develop novel antidepressants, as represented by clinical evidence of ketamine, a non-competitive NMDA receptor antagonist. Among glutamate receptors, mGlu2/3 receptors have also important roles in pathophysiology of depression, and we have reported that mGlu2/3 receptor antagonists exhibit antidepressant effects in several animal models. To date, we and others elucidated that AMPA receptor stimulation, followed by stimulation of BDNF-TrkB-mTOR pathways are involved in the antidepressant effects of mGlu2/3 receptor antagonists as observed with ketamine. In addition, both mGlu2/3 receptor antagonists and ketamine reportedly increased serotonin release in the medial prefrontal cortex (mPFC), through AMPA receptor stimulation. However, involvement of serotonergic system in antidepressant effects of mGlu2/3 receptor antagonists and ketamine has not been fully understood. In the present

study, we investigated roles of serotonergic system in the actions of mGlu2/3 receptor antagonists and ketamine.
Methods: Antidepressant effects of both LY341495 (an mGlu2/3 receptor antagonist) and ketamine were evaluated in both the novelty-suppressed feeding test (NSFT) and forced swimming test (FST) in mice. Involvement of serotonergic system was investigated by depleting serotonin by treating mice with PCPA, and by testing antagonists for 5-HT receptor subtypes. To identify the brain region involving in the effects, LY341495, ketamine or NBQX (an AMPA receptor antagonist) was dosed systemically as well as injected locally into the mPFC.
Results: Both LY341495 and ketamine dose-dependently reduced latency to feed in the NSFT, and reduced immobility time in the FST, both of which indicate antidepressant effects. As observed in other animal models, the antidepressant effects of LY341495 and ketamine in both tests were attenuated by systemic administration of NBQX, suggesting that AMPA receptor stimulation is involved in antidepressant effects of both compounds. Depletion of 5-HT with PCPA treatment abolished the antidepressant effects of LY341495 and ketamine in both tests. In addition, in the NSFT, the effects of LY341495 and ketamine were attenuated by WAY100635 (a 5-HT1A receptor antagonist) but not by ritanserin (a 5-HT2A/2C receptor antagonist). Likewise, CX546 (an AMPA receptor potentiator) significantly reduced latency to feed in the NSFT, and this effect was prevented by depletion of 5-HT and blockade of 5-HT1A receptor. Therefore, both compounds are suggested to exhibit antidepressant effects by AMPA receptor-dependent enhancement of serotonin release which subsequently stimulates 5-HT1A receptor. Interestingly, injection of NBQX into the mPFC attenuated antidepressant effects of systemic administration of LY341495 and ketamine in the FST, while NBQX injection itself was without effect. Moreover, injection of LY341495 or ketamine into the mPFC also exerted antidepressant effects in the FST, and these effects were abolished by 5-HT depletion.
Conclusions: These results suggest that increase in serotonergic activity (presumably increase in serotonin release and subsequent stimulation of 5-HT1A receptor) may be involved in antidepressant effects of both an mGlu2/3 receptor antagonist and ketamine, and that the action in the mPFC where both compounds stimulate AMPA receptor may be responsible for enhancement of serotonergic activity to exert antidepressant effects.
Keywords: ketamine, mGlu2/3 receptor, antidepressant, serotonin.
Disclosure: Taisho Pharmaceutical Co., Ltd.

W186. Identification of Novel Allosteric Dopamine Transporter Ligands with Nanomolar Potency

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Background: Published studies have identified novel allosteric modulators of the dopamine transporter (DAT). N-(diphenylmethyl)-2-phenyl-4-quinazolinamine (SoRI-9804), N-(2,2-diphenylethyl)-2-phenyl-4-quinazolinamine (SoRI-20040), and N-(3,3-Diphenylpropyl)-2-phenyl-4-quinazolinamine (SoRI-20041) partially inhibited [125I]RTI-55 binding and [3H]dopamine uptake, slowed the dissociation rate of [125I]RTI-55 from the DAT, and allosterically modulated d-amphetamine-induced DAT-mediated dopamine (DA) release. Over 500 analogs of these ligands were synthesized and evaluated for activity as allosteric modulators of DAT. We report here on 36 selected compounds.
Methods: Using synaptosomes prepared from rat caudate, we conducted [3H]DA uptake inhibition assays, DAT binding assays with [3H]WIN35428, and DAT-mediated release assays with either [3H]MPP + or [3H]DA.
Results: The initial set of compounds binned into three groups of [3H]DA uptake inhibitors: 1) full efficacy agents with a one-site fit, 2) full efficacy agents with a two-site fit and 3) partial efficacy agents with a one-site fit. We focused further studies on the partial efficacy uptake inhibitors. These agents were partial inhibitors of DAT, SERT, and NET uptake and much less potent at inhibiting DAT ([3H]WIN35428) binding. For example, SoRI-29574 partially inhibited DAT uptake with an $IC50 = 2.3 \pm 0.4$ nM, without affecting DAT binding. Overall, at concentrations less than 1 μM, these agents did not alter DAT-mediated [3H]MPP + release in the absence or presence of 100 nM d-amphetamine. At a dose 25-times greater than its IC50 for DAT uptake inhibition, SoRI-29574 had no significant effect on the d-amphetamine EC50 or Emax value for DAT-mediated release of [3H]MPP + . The full data set will be presented at the meeting.
Conclusions: These studies demonstrate the existence of potent DAT ligands that partially block DAT uptake, without affecting DAT binding or d-amphetamine-induced [3H]MPP + release. These compounds may prove to be useful probes of biogenic amine transporter function as well as novel therapeutics.
Keywords: dopamine transporter, allosteric modulator, cocaine, amphetamine.
Disclosure: Nothing to Disclose.

W187. Lisdexamfetamine-induced Suppression of Binge Eating in Rats is Attenuated by the α1 Adrenoceptor Antagonist, Prazosin

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Background: Binge-eating disorder (BED) is a common psychiatric condition, affecting ~2% of the adult population and presents as the frequent, compulsive, excessive consumption of highly palatable foods. We have recently developed and pharmacologically characterized a rat model of BED in which rats are given irregular, limited access to chocolate along with normal chow. Over a period of 4 weeks, rats develop robust, intermittent, hyperphagia of this palatable food. Lisdexamfetamine dimesylate (LDX) is a novel prodrug of d-amphetamine that is currently used for the treatment of attention-deficit/

hyperactivity disorder in children aged ≥6 years and adults. We have previously shown that LDX and its active metabolite d-amphetamine selectively reduced binge-eating of chocolate at low doses. The present study was conducted to determine the role of catecholamine receptors in the effects of LDX in this model of binge eating.
Methods: Female lean rats maintained on a reverse dark-light cycle were given free access to normal chow and water, and in addition were allowed brief (2h), irregular access to powdered chocolate over a period of 4 weeks. During this period, rats given intermittent access to chocolate developed robust binge eating behavior that consisted of profound hyperphagia of chocolate and reductions of normal chow intake on the days immediately following the binge sessions. Preliminary experiments to select doses for subsequent studies investigated the effects on chocolate and normal chow consumption of 6 doses of LDX (0.1 1.5 mg/kg po) and 5 doses of the antagonists, i.e. prazosin ([α1 adrenergic] 0.03-1.0 mg/kg ip), RX821002 ([α2 adrenergic] 0.03-1.0 mg/kg ip), SCH23390 ([D1] 0.01-0.5 mg/kg ip) and raclopride ([D2 dopaminergic] 0.02-0.5 mg/kg ip), given either 60 min (LDX, prazosin, RX821002 and raclopride) or 15 min (SCH23390) before the binge session. In the antagonist studies, LDX (1.0 mg/kg po) was administered followed by either vehicle (ip), prazosin (0.3 or 1.0 mg/kg ip), RX821002 (0.1 or 0.3 mg/kg ip), SCH23390 (0.1 or 0.3 mg/kg ip) or raclopride (0.1 or 0.5 mg/kg ip). Chocolate and normal chow intakes (kJ) were measured over the 2h binge period. Results are presented as mean chocolate intake (kJ) ± SEM; n = 10 rats/group. NS = not significantly different.
Results: LDX dose-dependently reduced the rats' consumption of chocolate in the 2 h binge session (vehicle = 197 ± 17; LDX[0.1] = 166 ± 18, NS to LDX[1.5] = 57 ± 7, $p < 0.001$), and in this experiment, LDX had no effect on the consumption of normal chow (vehicle = 6 ± 3; LDX[0.1] = 8 ± 2, NS to LDX[1.5] = 4 ± 2, NS). In the antagonist dose-finding study, none of the doses of prazosin or raclopride altered chocolate consumption, and it was only reduced by the highest doses of RX821002 (vehicle = 224 ± 10; RX[1.0] = 182 ± 12, $p < 0.05$) and SCH23390 (vehicle = 185 ± 17; SCH[0.5] = 133 ± 19, $p < 0.05$). The vehicle (po)/vehicle (ip) control level of chocolate consumption (veh/veh = 205 ± 19) was significantly decreased by 50% by LDX (1.0 mg/kg po) (LDX = 104 ± 13, $p < 0.001$). This effect was partially reversed in a dose related manner by prazosin (praz[0.3] = 145 ± 13, $p < 0.05$ vs LDX; praz[1.0] = 156 ± 12, $p < 0.01$ vs LDX). RX821002 (0.1 and 0.3 mg/kg ip), SCH23390 (0.1 and 0.3mg/kg ip) or raclopride (0.1 and 0.5 mg/kg ip) did not significantly modify the reduction of chocolate bingeing produced by LDX.
Conclusions: The results show that LDX dose-dependently and significantly reduced chocolate bingeing in binge-eating rats. Prazosin, RX821002, SCH23390 or raclopride did not affect chocolate intake at the doses used in the interaction studies. The effect of LDX on chocolate bingeing was partially reversed in a dose-related manner by prazosin, but not RX821002, suggesting LDX's effect is partially mediated by noradrenaline release acting through α1 but not α2 adrenoceptors. SCH23390 and raclopride did not significantly modify LDX's reduction of chocolate consumption, tentatively suggesting that this effect is not mediated by dopamine release acting through D1 or D2 receptors.
Keywords: Lisdexamfetamine, Binge eating, catecholamines.
Disclosure: P H Hutson is an employee of Shire Pharmaceuticals.

W188. Decynium-22 Enhances Social Behavior in Serotonin Transporter Knock-out Mice

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Background: Impaired social behavior is a core autism symptom that is generally treatment-resistant; this symptom also manifests frequently in other psychiatric disorders such as schizophrenia or major depression. Based on clinical findings and experiments in rodents, serotonin (5-HT) transmission is often disrupted in the socially-impaired brain, particularly in key areas shaping social behavior such as the frontal cortex and hippocampus. Selective serotonin reuptake inhibitors (SSRIs) such as Prozac (fluoxetine) are capable of enhancing sociability in limited patient subpopulations, but their efficacy is greatly diminished if 5-HT transporter (SERT) function is compromised. For this reason, our goal was to characterize the effects of blocking ancillary transporters of 5-HT instead of the SERT. These auxiliary transporters, known as 'uptake 2', include organic cation (OCT) and plasma membrane monoamine transporters (PMAT) which both exhibit lower affinity but greater capacity than SERT to remove 5-HT from extracellular fluid.
Methods: Through synaptosomal uptake and radioligand binding studies, the affinity of the pseudoisocyanine decinium-22 (D-22) for SERT and its ability to block 5-HT uptake in vitro was examined and compared to selective 5-HT reuptake inhibitors such as fluoxetine. SERT knock-out (-/-) mice, which exhibit impaired social behavior relative to wild-type littermates, were utilized to examine both the acute (i.p. injection) and chronic (2 weeks of administration via sub-cutaneous osmotic pumps) effects of uptake 2 blockade by D-22 on social behavior. Finally, the pharmacokinetics of D-22 under behaviorally-relevant conditions were characterized.
Results: D-22 effectively blocked 5-HT uptake (Km = 92 ± 12 nM) in SERT +/+ mice, but yet it had negligible affinity for the SERT (Ki > 3000 nM). Systemically administered D-22 (1 mg/kg) cleared from mouse serum with a half-life of roughly 30 min. Within 1 hour of D-22 (0.01 mg/kg) administration social sniffing increased significantly in SERT -/- mice, relative to vehicle-controls ($p < 0.5$, N = 10-12). Within 4 hours of D-22 administration, this effect was extinguished. Two weeks of D-22 (0.001 mg/kg/d) administration improved SERT -/- sociability in three-chambered tests in a manner similar to the 1 hour acute administration, with no apparent adverse effects in SERT -/- mice.

Conclusions: Blockade of uptake 2 transporters appears to be an effective short or long-term treatment strategy for impaired social behavior that warrants further study.
Keywords: sociability, autism, transporters, uptake 2.
Disclosure: Nothing to Disclose.

W189. Combinations of Buprenorphine and Samidorphan Modulate Glutamatergic Transmission in the Medial Prefrontal Cortex and Ventral Hippocampus of Male Wistar Rats

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Background: The endogenous opioid system is thought to play a key role in the regulation of mood, however, the mechanism is uncertain. ALKS 5461 is a balanced opioid modulator that represents a novel treatment for depression that combines buprenorphine (BUP), a partial mu agonist, with samidorphan (SAMI), a potent mu antagonist. We previously described that combinations of BUP and SAMI modulate mesolimbic monoaminergic systems, and produce antidepressant-like behavioral effects in rats. These nonclinical microdialysis studies were designed to further investigate the effects of BUP, alone and in combination with SAMI, on extracellular concentrations of glutamate (Glu) and γ-Aminobutyric acid (GABA) in the medial prefrontal cortex (mPFC) and ventral hippocampus (vHIPP) of male Wistar rats.
Methods: Rats were maintained on a 12-hr light/dark cycle with unrestricted access to food and water. Two sets of experiments were conducted to determine the effects of: 1) BUP alone (0.1 mg/kg) and 2) a fixed dose of BUP (0.1 mg/kg) with ± SAMI (either 0.3 or 3.0 mg/kg) on extracellular concentrations of Glu or GABA in the mPFC and vHIPP. Animals were administered test article subcutaneously at a dose volume of 1 mL/kg. Both experiments utilized a vehicle (saline) control group. Microdialysis probes were inserted into the mPFC and vHIPP using the following coordinates from bregma: A/P + 3.40; M/L ± 0.8; D/V -5.0 or A/P -5.3; M/L ± 4.80; D/V -7.5 respectively. Probe placement was verified in all rats at the end of the study. Bioanalytical analysis of GABA and Glu was performed using either an HPLC-MS/MS (AB Sciex Qtrap 5500) or a UHPLC-EC (Antec Leyden ALEXYS). The amount of each analyte was quantified "on column" per µl of sample. Data analysis was performed by either a two-way repeated measures ANOVA, or an ANCOVA with log(baseline) as a covariate.
Results: In the initial experiment, extracellular concentrations of Glu within the mPFC gradually increased to a maximum of 135% above baseline over the 4.5 hours following a single subcutaneous dose of BUP (0.1 mg/kg). In the second experiment, BUP significantly increased extracellular Glu levels within the mPFC two to three hours after drug administration. The maximal increase in mPFC Glu produced by BUP was approximately 190% above baseline levels. Concurrent administration of SAMI dose-dependently attenuated, but did not completely block the effects of BUP on Glu concentrations in the mPFC. Neither BUP given alone, nor in combination with SAMI, affected mPFC concentrations of GABA. In the vHIPP, extracellular Glu concentrations decreased slightly over time, following BUP administration. Administration of BUP in combination with the low dose of SAMI resulted in a further reduction in vHIPP Glu concentrations over time. The maximal decrease in vHIPP Glu produced by the combination occurred two to three hours after administration and resulted in Glu concentrations approximately 50% below vehicle treated levels. Administration of the high dose of SAMI with BUP reversed this effect, resulting in Glu concentrations similar to the vehicle-treated group. Neither BUP alone, nor in combination with SAMI, affected vHIPP concentrations of GABA.
Conclusions: Dysregulation of the endogenous opioid system has been postulated to play an important role in mood disorders. Exogenous opioids, including BUP, have been shown to have beneficial effects in treating depression. In these studies, BUP produced a late increase in extracellular concentrations of Glu, which was modulated, but not completely blocked, by SAMI. The lower-dose combination of BUP and SAMI also decreased vHIPP Glu concentrations. Given the temporal pattern, the glutamatergic effects of BUP and SAMI in the mPFC and vHIPP likely occur via indirect pathways. In addition to the glutamatergic effects reported here, we previously found that the combination of BUP (0.1 mg/kg) and SAMI (0.3 mg/kg) modulated mesolimbic monoaminergic systems, decreased immobility time in the forced swim test and increased saccharine consumption in nonclinical rat models. Taken together, these results indicate that balanced modulation of monoaminergic and glutamatergic systems may contribute to the efficacy of ALKS 5461 in the treatment of depression.
Keywords: ALKS 5461, Buprenorphine, Samidorphan, Glutamate.
Disclosure: David J. Eyerman, Jacobi I. Cunningham, Reginald L. Dean and Daniel R. Deaver are full-time employees of Alkermes, Inc. Helen L. Rowley and David J. Heal are full-time employees of Renasci Ltd. All studies were funded by Alkermes, Inc.

W190. Characterization of c-Jun N-Terminal Kinase (JNK)-mediated Mechanisms of Cannabinoid and Opioid Tolerance

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Background: Desensitization of G protein-coupled receptors (GPCRs) is one mechanism by which tolerance to GPCR-directed agonists can develop. Mice expressing a desensitization-resistant form of the cannabinoid receptor 1 (CB1) receptor were produced to investigate the role that CB1 receptor desensitization plays in tolerance to cannabinoid drugs in vivo. These mice express a form of CB1 where putative G protein-coupled receptor kinase (GRK) phosphorylation sites at serine residues 426 and 430 have been mutated to non-phosphorylatable alanines (S426A/S430A).

Previous reports have demonstrated that c-Jun N-terminal kinase (JNK) signaling is responsible for acute tolerance to the antinociceptive effects of 10 mg/kg morphine but not 0.3 mg/kg fentanyl. This study also examined the role of JNK signaling in the development of chronic tolerance to cannabinoid and opioid agonists.
Methods: The antinociceptive effects of 30 mg/kg delta-9-THC, 10 mg/kg morphine, and 0.3 mg/kg fentanyl were examined using the hotplate and tail-flick tests. Drug-induced hypothermia was also assessed by measuring body temperature. Baseline measurements were taken prior to and also 60 minutes after each daily drug administration. Morphine and fentanyl injections were administered once daily as sub-cutaneous injections while delta-9-THC was administered via intraperitoneal injection. For experiments examining the role of JNK signaling in tolerance, the JNK inhibitor SP612005 was administered by intraperitoneal injection 60 minutes prior to delta-9-THC, morphine, or fentanyl injection. RNA samples for microarray analysis or quantitative real time PCR (qPCR) were isolated from dorsal root ganglia (L4-L6), striatum, and hypothalamus of S426A/S430A mutant mice treated with vehicle, 3 mg/kg SP600125, 30 mg/kg delta-9-THC, or SP600125 and delta-9-THC. Tissues were extracted and lysed in QIAzol lysis reagent with stainless steel balls using a TissueLyser at 25hz for 90 seconds. RNA was isolated with a Qiagen RNeasy Mini Prep kit. RNA concentrations were determined using a NanoDrop spectrophotometer. For microarray, RNA samples were amplified, reverse transcribed to cDNA, labeled and hybridized to a high density Nimblegen (Roche) array containing 135,000 long oligos (60-mers) representing the entire mouse genome. Validation of microarray candidates was done by qPCR using TaqMan probes.
Results: In this study we found that CB1 desensitization-resistant S426A/S430A mutants exhibited enhanced and prolonged hypothermic and antinociceptive responses to delta-9-THC, endocannabinoids, and the synthetic cannnabinoid CP 55,940. S426A/S430A mutants exhibited a significant but modest delay in tolerance to delta-9-THC and CP 55,940. Pre-treatment of wild-type mice with 3 mg/kg SP600125 also caused a delay in the development of tolerance to antinociceptive effects of daily 30 mg/kg delta-9-THC injections. In contrast, pre-treatment of S426A/S430A mutant mice with 3 mg/kg SP600125 caused a block in the development of tolerance to the antinociceptive effects of delta-9-THC. Tolerance to delta-9-THC was not altered in S426A/S430A mutant mice also lacking either JNK 1 or JNK2. Putative JNK targets involved in delta-9-THC tolerance that were identified by microarray analysis including CB1, Fabp7, and Cx3cr1 were validated by qPCR. The role of JNK signaling in the development of chronic tolerance to morphine and fentanyl was also examined. Pre-treatment with either 3 or 10 mg/kg SP600125 attenuated tolerance to the antinociceptive effects of 10 mg/kg morphine but not 0.3 mg/kg fentanyl in the tail-flick and hotplate tests. Interestingly, pre-treatment with SP600125 attenuated tolerance to the hypothermic effects of both morphine and fentanyl. Tolerance to chronically administered 10 mg/kg morphine was abolished in JNK 1 knock-out (KO) mice.
Conclusions: This work suggests that the "classic" GRK/arrestin mechanism of CB1 desensitization is responsible for the magnitude and duration of acute physiological responses to delta-9-THC. The finding that tolerance to delta-9-THC is prevented in S426A/S430A mutant mice treated with SP600125 demonstrates that coordinated action of both JNK and GRK/arrestin signaling is responsible for chronic tolerance to delta-9-THC. The finding that tolerance to the hypothermic effects of fentanyl is modestly attenuated by SP600125 was surprising and suggests that JNK signaling might be involved in tolerance for certain physiological responses to fentanyl. Prior studies have shown that JNK 2 is essential for acute tolerance to morphine. However, we found that chronic tolerance for morphine was prevented in mice lacking JNK 1. This unexpected finding raises the possibility that different JNK isoforms may be responsible for distinct types of morphine tolerance. Taken together these collective results demonstrate the important role that JNK signaling plays in chronic tolerance for agonists acting at two different G protein-coupled receptors (CB1 and mu opioid receptor).
Keywords: cannabinoid, opioid, THC, tolerance.
Disclosure: Nothing to Disclose.

W191. Preclinical Characterization and Functional Mechanism of ASP5736, a Selective Serotonin 5-HT5A Receptor Antagonist with Potential Utility for the Treatment of Schizophrenia and Affective Disorders

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Background: The 5-HT5A receptor is a G-protein-coupled seven-transmembrane receptor expressed to a high degree in the central nervous system, including the hippocampus, thalamus, amygdala, and cerebral cortex, and to a low degree in peripheral tissues. 5-HT5A receptor knockout mice exhibit increased exploratory behavior in novel environments, which, in conjunction with its widespread localization pattern, suggests that this receptor is involved in mood, affective disorder, and cognitive function. Here, we used electrophysiological, biochemical, and behavioral methods to investigate the effects of the novel and selective 5-HT5A receptor antagonist ASP5736 in rats. Current results have uncovered new function of 5-HT5A, and also strongly suggested potential benefit of ASP5736 for the treatment of cognitive impairment as well as mood dysregulation in schizophrenia and affective disorders.
Methods: Occupancy: Male Wistar rats were treated with ASP5736, and dissected olfactory bulbs were frozen and cut into coronal sections. Sections were pre-treated with spiperone and clozapine with or without 5-HT. The binding of [125I]-lysergic acid diethylamide (LSD) was analyzed using autoradiography. Functional assay (cAMP): Native or 5-HT5A-receptor-expressing HEK293 cells were transfected with a GloSensorTM plasmid. After being incubated with luciferin, cells were treated with ASP5736 and forskolin in the presence of the 5-HT7 antagonist SB269970. Five-carboxamidotryptamine (5-CT) was applied, and luminescence was monitored. In vivo electrophysiological experiments: Male SD rats were anesthetized with chloral hydrate

and the tips of the electrodes were broken to yield an impedance of 2-4 MΩ at 135 Hz. A hole was drilled in the skull, for dopaminergic (DAergic) neurons 3.2 mm anterior of the interaural line and 0.7 mm lateral to the midline (Paxinos and Watson 2007). Presumed DAergic neurons were found 7.5–9.0 mm below the brain surface and were recognized by their characteristic triphasic action potential waveform of more than 2.0 ms duration, basal firing rates of 1–10 Hz, and frequent occurrence of burst firing (Wang 1981). Microdialysis: Male Long-Evans rats were sub-chronically treated with PCP (2 mg/kg, b.i.d.) or saline. During a 7-day washout period, rats underwent surgery for implantation of a guide cannula in the mPFC. On the day of microdialysis study and after the administration of ASP5736 or vehicle, an object (made of LEGO®s) was presented for cognition-related stimulation. DA was measured using HPLC with ECD, and GABA was measured via liquid chromatography-mass spectrometry (LC/MS). Attentional set-shifting task (ASST): Under the same conditions as the microdialysis study, executive function was assessed by ASST using a modified version of a previously described protocol (Birrell and Brown 2000: Rodefer 2005).

Results: 1) An ex vivo receptor occupancy study showed that ASP5736 replaced the binding of [125I]-LSD to 5-HT5A receptors in the olfactory bulb of rats at behaviorally effective doses. 2) ASP5736 exhibited concentration-dependent antagonism of the 5-CT-induced decrease in cAMP levels in forskolin-treated HEK293 cells stably expressing the 5-HT5A receptor. 3) IHC study showed that 5-HT5A receptors were expressed in DAergic neurons and parvalbumin (PV)-positive interneurons in the VTA, a nucleus of origin of DAergic neurons, and in PV-positive interneurons in the mPFC. 4) An electrophysiological study showed that, for DA cells in the parabrachial nucleus (PBP), burst firing significantly increased following ASP5736 treatment. However, for DA cells in the paranigral nucleus, no significant differences were noted in either firing rate or burst firing following treatment with ASP5736. 5) An in vivo brain microdialysis study showed that ASP5736 increased extracellular levels of DA and GABA in mPFC of sub-chronically PCP-treated rats exhibiting decreased levels of these neurotransmitters. 6) ASP5736 significantly ameliorated the extradimensional shift deficit in ASST induced by subchronic PCP treatment in rats.

Conclusions: Our results suggest that ASP5736 increases the release of DA in the mPFC by blocking 5-HT5A receptors on VTA DAergic neurons projecting to the mPFC and GABA by blocking 5-HT5A receptors on GABAergic interneurons located in mPFC. ASP5736 also activates VTA DA neurons, particularly those located in the PBP that largely, but not exclusively, project to the prefrontal cortex. In the present study, ASP5736 preferentially stimulated the burst firing mode of DA cells, which is a major determinant of the mechanism of DA D1 receptor-dependent signaling in DA target areas that is involved in the control of working memory. Our preclinical results obtained with ASP5736 support a pro-cognitive effect as well as potential mood-elevation effects for this compound. ASP5736 might be clinically effective for treating patients with schizophrenia.

Keywords: 5HT5A receptor antagonist, schizophrenia, dopamine, GABA.

Disclosure: Mayako Yamazaki, Junko Yarimizu, Katsuya Harada, Noriyuki Yamamoto, Mayuko Okabe, Keni Ni and Mitsuyuki Matsumoto are employees of Astellas Pharma Inc.

W192. The NMDA Antagonists AZD6765 and Ramacemide Eliminate Apneic Breathing in a Mouse Model of Rett Syndrome

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Background: Patients with Rett syndrome (RTT), a severe disorder caused by mutations in the MECP2 gene exhibit postnatal neurological regression leading to motor and cognitive impairments, respiratory and autonomic dysregulation, seizures and autism-like behaviors. Studies in the Katz laboratory demonstrated that a sub-anesthetic dose of the non-selective NMDA antagonist ketamine acutely reverses cortical hypofunction in Mecp2 null and heterozygous mice (Kron et al., 2012), suggesting the potential utility of NMDA antagonists for treatment of RTT. Therefore, the present study was designed to evaluate more selective NMDA antagonists in rodents for their ability to alleviate symptoms likely to be of clinical relevance for RTT patients. In particular, we examined AZD6765, a low trapping NMDA antagonist, remacemide and its active metabolite, desglycinyl remacemide, which are moderate to low affinity (0.5 to 68 uM) NMDA channel blockers previously in clinical development for the treatment of treatment resistant depression, epilepsy and ischemic brain damage.

Methods: Behavioral and physiological testing in wild-type rats and mice (seizure suppression, EEG-biomarker, anxiety/depression) and Mecp2tm1.1Jae mutant mice (plethysmographic analysis of breathing) were used to characterize the potential utility of AZD6765, remacemide and desglycinyl remacemide for the treatment of RTT symptoms.

Results: Studies in wildtype animals demonstrated that AZD6765, remacemide and desglycinyl remacemide attenuate electroconvulsive-induced seizures (MES-test) and reduce the acute stress response in a forced-swim test at doses (8-30 mg/kg) associated with measurable changes in cortical gamma band EEG. Furthermore, all compounds acutely reverse the apneic breathing phenotype in Mecp2 mice at doses corresponding to clinically relevant and well tolerated exposures. Specifically, a single intraperitoneal injection of AZD6765 (3 mg/kg), remacemide (60 mg/kg) or desglycinyl remacemide (30 mg/kg) in 12-16 week old female heterozygous Mecp2tm1.1Jae mice reduced spontaneous apneas (defined as respiratory pauses longer than twice the average duration of expiration) to wildtype levels within 3 hours of treatment.

Conclusions: These preliminary studies, combined with human data demonstrating positive effects of AZD6765 on depression and anxiety symptoms (Sanacora et al., 2013) and remacemide as an adjunctive treatment for refractory epilepsy (Baesag et al., 2001; Chadwick et al., 2002; Devinsky et al., 2002) suggest that the low trapping

NMDA antagonists with a low propensity to produce dissociative side effects, and related compounds, may have therapeutic value in the treatment of RTT patients. (Supported by grants from the Rett Syndrome Research Trust and AstraZeneca Pharmaceuticals to DMK).
Keywords: Rett Syndrome, NMDA Antagonists, AZD6765, MeCP2.
Disclosure: Nothing to Disclose.

W193. Oxytocin Blocks Stress-induced Reinstatement of Cocaine Seeking: Inter-individual Predictions of Efficacy in Yohimbine-potentiated Footshock-induced Relapse Behavior

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Background: Stressful life events can trigger a relapse to drug taking. Oxytocin is a potential treatment that has been shown in clinical studies to attenuate subjective and physiological markers of stress and drug craving. Similarly, oxytocin has also been shown to block stress-induced reinstatement of methamphetamine seeking in an animal model of relapse. However, stress as typically applied in animal studies (e.g., footshock) tends to produce weak reinstatement behavior, and oxytocin has not been tested as a treatment for stress-induced cocaine seeking. Hence, the extent to which oxytocin plays a role in stress-induced reinstatement of cocaine seeking is unknown, as oxytocin may not block robust stress-induced reinstatement that is more representative of the clinical situation. We tested the ability of oxytocin pretreatment to block high levels of stress-induced reinstatement of cocaine seeking elicited by using yohimbine to potentiate the stress effects of footshock.
Methods: Active lever pressing was extinguished in animals trained to self-administer cocaine. Animals were then pretreated with either oxytocin (1 mg/kg) or vehicle 30 min prior to reinstatement testing. Animals were stressed with yohimbine pretreatment (2.5 mg/kg; 30 min prior to session start), 20 min of unpredictable footshock (0.80 mA), or both. Responding on the previously active lever was then recorded for 120 min.
Results: Yohimbine or footshock alone failed to elicit significant reinstatement of cocaine seeking. However, active lever responding was robustly reinstated when these modalities were combined. Moreover, oxytocin pretreatment blocked this reinstatement in proportion to the magnitude of reinstatement with vehicle pretreatment.
Conclusions: Thus, yohimbine and footshock pretreatment interact synergistically to produce robust stress-induced reinstatement, and oxytocin is an efficacious method of blocking this multimodal relapse behavior, indicating strong clinical potential as a relapse-prevention medication.
Keywords: Cocaine, Reinstatement, Oxytocin, Yohimbine.
Disclosure: Nothing to Disclose.

W194. A Novel Ghrelin Receptor Antagonist May Serve as a Therapeutic Target for Alcoholism

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Background: Ghrelin is a gut-brain peptide that stimulates appetite and food intake. Preclinical and human evidence suggests ghrelin activity correlates with increased alcohol craving and consumption. Antagonizing its receptor, ghrelin receptor 1a (GHSR1a), has been linked with decreased alcohol reward and use in preliminary studies in mice, an observation not translated yet in humans. The goal of this project is to test the safety, efficacy, and effects on ethanol-induced behavior of a novel GHSR1a antagonist (PF-05190457) as a potential treatment for alcoholism.
Methods: Optimal dose and time of the GHSR1a antagonist was determined by measuring plasma and brain levels of PF-05190457 at various concentrations (0.3, 1, 3, 10, 30 mg/kg; intraperitoneally) and times (15 and 60 min) in Wistar rats. Next, ethanol sensitivity and drug-ethanol interactions were measured by locomotor activity. Lastly, the effect of PF-05190457 on ethanol-induced loss of the righting reflex (LORR) was determined.
Results: The optimal dose and time to reach 50% and 100% GHSR1a occupancy was 3 and 10 mg/kg, respectively, at a 60 minute time point. Hereinafter, our studies focused on the 3 and 10 mg/kg concentration and the 60 min time point to determine safety and efficacy of PF-05190457. Our results confirm our hypothesis that PF-05190457 has no significant effect on safety: drug-ethanol interactions or ethanol-induced behavioral measures. More specifically, we did not observe a sedative response in the locomotor activity task or LORR at both drug concentrations. Notably, we observed a non-significant trend toward decreased alcohol sensitivity in the higher doses of PF-05190457 (10mg/kg). We are currently determining the effects of PF-05190457 on ethanol reward and ethanol-induced behavior by examining the effects on ethanol-induced ERK phosphorylation in a multitude of brain regions and self-administration, extinction, and cue- and stress-induced relapse.
Conclusions: We successfully confirmed the safety of this compound in our rodent model and are currently carrying out our planned human studies. Based on previous preclinical literature with GHSR1a antagonists and our current ongoing investigation, PF-05190457 appears to be a promising and safe candidate for the treatment of alcoholism.
Keywords: Alcoholism, Ghrelin, Pharmacology, Behavior.
Disclosure: Nothing to Disclose.

W195. Gaba-B Receptor Agonist R-Baclofen Reverses Social Deficits and Reduces Repetitive Behavior in Two Mouse Models of Autism

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Background: Autism spectrum disorder is diagnosed by two core behavioral criteria, unusual reciprocal social interactions and communication, and repetitive behaviors with restricted interests. Excitatory/inhibitory imbalance is a prominent hypothesis for the etiology of autism. Reductions in excitatory glutamatergic neurotransmission with antagonists and negative modulators, and increases in inhibitory neurotransmission with GABAergic agonists and positive modulators, have reversed abnormalities in mouse models of autism and Fragile X syndrome on synaptic plasticity, spine morphology, seizures and behavioral phenotypes (Kreuger and Bear, 2011; Silverman et al., 2013; Vorstman et al., 2014). Initial clinical trials with STX209 (Arbaclofen) yielded variable but promising results on the ABC-Social Avoidance, Vineland II-Socialization, Social Responsiveness and ABC-irritability scales (Berry-Kravis et al., 2012; Erickson et al., 2014).
Methods: We tested the hypothesis that activation of the GABA-B receptor with the commercially available r-baclofen enantiomer, but not the less potent s-baclofen enantiomer, would rescue autism-relevant phenotypes in the BTBR and C58/J inbred strain mouse models of idiopathic autism. BTBR display well-replicated deficits in sociability and long bouts of repetitive self-grooming. C58/J exhibit high levels of stereotyped vertical jumping. Behavioral assays were conducted after a single acute dose of r-baclofen or vehicle. Tests included (a) observations of stereotyped and repetitive behaviors, (b) 3-chambered social approach, and (c) open field locomotion as a control for potential sedation or hyperactivity confounds.
Results: Two independent cohorts of BTBR showed improved social approach following acute r-baclofen treatment. BTBR displayed reductions in repetitive self-grooming behavior after r-baclofen. C58/J displayed reductions in stereotyped jumping behavior after r-baclofen. Open field activity was not significantly affected by r-baclofen doses that increased sociability and decreased stereotyped and repetitive behaviors.
Conclusions: Our findings report beneficial effects of r-baclofen in two inbred strains of mice with endogenous behavioral phenotypes relevant to the two diagnostic criteria for autism spectrum disorder. These results support further investigations of the GABA-B agonist target, in other preclinical models and in further clinical studies, to evaluate the benefits of enhancing inhibitory synaptic transmission to treat the core diagnostic symptoms of autism.
Keywords: autism, social behavior, repetitive behavior, GABA.
Disclosure: Nothing to Disclose.

W196. Novel Selective D3/5-HT2A Receptor Antagonists: Efficacy in Cognitive and Antipsychotic Animal Paradigms with a Differentiated Functional (f)MRI Profile

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Background: Schizophrenia is associated with cortical glutamatergic hypofunction and striatal dopaminergic hyperfunction, as well as altered serotonergic tone. D3 and 5-HT2A receptors (R's) are highly expressed in the dopaminergic basal ganglia and glutamatergic cortico-striatal pathways, which are thought to be dysfunctional in schizophrenia. Selective 5-HT2A and D3R antagonists are active in different behavioural paradigms used to predict antipsychotic-like efficacy, and improve social and spatial cognition. The current study describes the in vitro and in vivo pharmacological characterization of the first potent combined D3/5-HT2A antagonists and compares their selectivity activity and side effects with current antipsychotic drugs.
Methods: Human (h)5-HT2A R, D3 R and D2 R in vitro affinity was determined using radioligand binding in transiently transfected HEK-EBNA cells. Selectivity and species screens for h, rat and monkey Rs, used transiently transfected receptors and radioligand binding. Functional activity was assessed using quinpirole-induced [35S]GTP□S for human D2 and D3 Rs and 5-HT-induced Ca2 + fluorescence (FLIPR) and phospho-inositol hydrolysis for 5-HT2A Rs (Kb and pA2). Compounds were tested in vivo, following oral administration. Paradigms included, but were not restricted to: reversal of amphetamine (2.5 mg/kg, s.c.) and ketamine (0.03 mg/kg, s.c.) induced locomotor activity (LMA) in mice; MK801 (0.03 mg/kg, s.c.) induced effects in 5-choice serial reaction time (5-CSRT) in rats; differential reinforcement of low rate responding (DRL) in monkey, object recognition (OR) after subchronic phencyclidine (sc-PCP; 3 mg/kg i.p. 2x/day for 7 days, then 7 days drug free) in rats and assessment of catalepsy in both rats and monkeys. 5-HT2A receptor occupancy was assessed in rat using ex vivo [3H]M100907 radioligand binding. The neural activity pattern was determined using fMRI.
Results: Multiple compounds were assessed and found to be high affinity competitive antagonists for both hD3 and 5-HT2A receptors, with greater selectivity at 5-HT1D, 5-HT2C, 5-HT6, 5-HT7, D1, D2, H1, M1 and M3Rs compared to antipsychotic drugs. The 5-HT1A R was occasionally an exception with some compounds being partial agonists. For example, binding affinity (Ki) for RO5463418 was 4, 2, 74, 1033 nM and RO6805403 was 5, 5, 287, 13 nM for hD3, 5-HT2A, D2, and 5-HT1A Rs respectively. There were minimal species differences between human, rat and monkey. RO5463418 and RO6805403 at 1 mg/kg reversed

amphetamine and ketamine-induced LMA in mice, RO5463418 (3 mg/kg) and RO6805403 (0.1 mg/kg) reversed MK801-induced impulsivity in the 5-CSRT and increased reinforcements in monkey DRL (1 mg/kg). In a cognition study, RO6805403 (1 mg/kg) reversed deficits in object recognition following cessation of scPCP in rats. Catalepsy was only observed at doses above efficacious doses in rats and monkeys. Radioligand binding ex vivo, using [3H]M100907, indicated dose dependent 5-HT2A R displacement in cortex, nucleus accumbens, ventral pallidum and fundus striati. An acute fMRI study with RO6805403 showed some activity changes similar to other antipsychotics (eg. thalamus, mPFC), but differentiated in other brain regions (e.g. insular and parietal cortices, dorsal striatum, dorsal hippocampus).
Conclusions: D3/5-HT2A receptor antagonists modified both dopaminergic and glutamatergic activity in behavioural paradigms. To achieve selectivity across the biogenic amine receptors proved to be challenging, yet was successful. The compounds showed promising antipsychotic-like and procognitive effects in behavioural paradigms, as well as a differentiated fMRI profile from other antipsychotics.
Keywords: antipsychotic, D3 receptor, 5-HT2A receptor, serotonin 2A.
Disclosure: Employee of F. Hoffmann-La Roche, Roche Innovation Center Basel.

W197. Behavioral Alterations and Dependence Following Acute and Chronic Exposure to Cannabis Smoke

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Background: Cannabis (marijuana) is the most widely used illicit drug in the US, and consumption among adolescents and young adults is rising. Animal studies have shown that adolescent exposure to delta 9-tetrahydrocannabinol (THC) or synthetic CB1 receptor agonists causes alterations in cognition and measures of anxiety- and depression-like behavior upon maturation to adulthood. It is not known, however, whether similar alterations result from exposure to cannabis via smoking, which is the most common route of administration in humans. As a first step toward pursuing these questions, the goal of these studies was to develop a rat model of cannabis smoke exposure and to determine how acute and chronic exposure to cannabis smoke influences motor activity and measures of dependence.
Methods: Smoke was generated by burning cannabis cigarettes (5.3% THC, NIDA Drug Supply) using an automated cigarette smoking machine. During exposure sessions, adult male Wistar rats were placed with their cagemates into clean standard rat cages with wire lids, which were then placed into the smoke exposure chamber ($n = 10$) or air control condition ($n = 10$). Rats were exposed to these conditions for 1 h/day, 5 days/week, for 8 weeks. These exposure conditions produced cannabis smoke at a concentration of about 400 total suspended particulate (TSP)/m3, and CO levels of about 200 ppm (below the threshold for known adverse effects). We investigated the effects of cannabis smoke on development of dependence and on locomotor activity in a small open field (40 x 40 cm), a large open field (120 x120 cm), and the elevated plus maze. In order to determine serum THC levels, blood samples were collected immediately after smoke exposure during weeks 2 and 4, and THC levels were assessed using a THC ELISA kit. During week 2, rats were also tested in a small open field immediately following smoke exposure. During week 3, somatic withdrawal signs were recorded after administration of the CB1 receptor antagonist SR 141716A (rimonabant, 5 mg/kg, i.p) or vehicle. During week 4, the effects of SR 141716A (5 mg/kg) or vehicle on behavior in the small open field were investigated. Weeks 7 and 8 investigated effects of cannabis smoke on anxiety-like behavior. During week 7, rats were tested in the elevated plus maze at both 48 h after the last smoke exposure and again the following day immediately after smoke exposure. During week 8, rats were tested in a large open field (120 x 120 cm) at both 48 h after the last smoke exposure and again the following day immediately after smoke exposure.
Results: Cannabis smoke exposure led to serum THC levels of 170 ng/ml (week 2,171.5 $\pm$ 3.1 ng/ml; week 4, 169.5 $\pm$ 6.4 ng/ml), which is similar to levels observed in studies of human cannabis smokers. Exposure to cannabis smoke did not affect ambulation (total distance traveled) in the small open field but decreased the number of horizontal beam breaks and vertical beam breaks (rearing) relative to control rats. A more detailed analysis indicated that cannabis smoke increased ambulation and horizontal activity during the first 5 min but decreased these parameters at later time points. Following SR 141716A administration, cannabis rats showed more somatic withdrawal signs than control rats, suggesting that passive exposure to cannabis smoke lead to changes in CB1 receptor signaling and possibly cannabis dependence. SR 141716A also increased ambulation and horizontal activity in both cannabis and control rats, and prevented the cannabis smoke-induced decrease in vertical activity (rearing). There were no differences in the behavior of cannabis and control rats in the large open field or the elevated plus maze test 48 h after their last smoke exposure session. When the rats were tested for a second time immediately after smoke exposure, however, cannabis rats traveled a greater distance in both the large open field and the elevated plus maze. The latency to enter the center of the large open field was decreased, which might have been due to the increase in locomotor activity. Cannabis smoke exposure did not affect open arm entries or time on the open arms in the elevated plus maze.
Conclusions: Taken together, these data show that acute exposure to cannabis smoke leads to an increase in serum THC levels and alterations in motor activity, and that repeated exposure produces signs of cannabis dependence as indicated by the presence of antagonist-precipitated withdrawal symptoms. These findings are similar to those from earlier studies using other cannabis smoke exposure models (and are analogous to results from our previous work with tobacco smoke exposure), and suggest that the freely-moving exposure conditions employed here will be useful for determining how developmental exposure to

cannabis smoke affects neurobehavioral and neuroimaging outcome measures.
Keywords: cannabis, marijuana, smoking, dependence.
Disclosure: Nothing to Disclose.

W198. Therapeutic Efficacy of M1 Acetylcholine Receptor Positive Allosteric Modulation on Deficits in Cortical Plasticity and Behaviors in a Chronic Phencyclidine-treated Mouse Model of Schizophrenia

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Background: Current medications available provide efficacy in reducing the positive symptoms associated with schizophrenia but provide little to no efficacy in reducing negative symptoms and cognitive impairments. The magnitude of deficits in cognitive function, as well as social withdraw and apathy associated with negative symptoms, is directly correlated to the patients' inability to successfully integrate into society. Therefore, a critical need exists for new treatments directed towards these specific symptoms. Deficits in acetylcholine (ACh) neurotransmission in the cortex have been implicated in both the cognitive impairments and negative symptoms. The effects of ACh on cortical pyramidal neurons are largely mediated by muscarinic ACh receptor subtype 1 (M1) receptors. A clinical study conducted in schizophrenia patients suggests that the M1/4-preferring agonist xanomeline may have efficacy in reducing all three symptom clusters observed in schizophrenia patients. Unfortunately, xanomeline failed to advance in clinical development due to a lack in subtype selectivity, resulting in profound adverse effects associated with activation of M2/3 receptors. In recent years, we have developed potent positive allosteric modulators (PAMs) of M1 that provide true subtype selectivity and are now advancing in preclinical and clinical development. These compounds also possess excellent pharmacokinetic profiles with significant brain penetration, providing an unprecedented opportunity to evaluate the in vivo efficacy of selective M1 PAMs in preclinical models of schizophrenia. Chronic NMDA receptor antagonism using phencyclidine (PCP) has been shown to be a reliable model to recapitulate the negative and cognitive symptoms of schizophrenia. Therefore, we utilized PCP-treated mice as a preclinical model to test the hypothesis that selective potentiation of M1 can restore deficits in medial prefrontal cortex-mediated synaptic plasticity, cognitive impairments and social interaction.
Methods: All animal studies were approved by the Vanderbilt University Medical Center 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. Six week old C57Bl/6 male mice were administered 10 mg/kg phencyclidine (1 mg/ml, saline) subcutaneously, once daily for seven consecutive days. After a seven day washout period, mice underwent electrophysiology or behavioral studies. For carbacol (CCh)-induced muscarinic long term depression (mLTD) studies, brain slices were incubated with CCh + /- M1 PAM, VU0453595, via bath application and excitatory postsynaptic currents (EPSCs) were measured in the Layer II/III to layer V synapse of the medial prefrontal cortex (mPFC). To investigate the in vivo efficacy of VU0453595 in mPFC-mediated forms of cognitive function and social behaviors in a preclinical rodent model of schizophrenia, mice were pretreated with VU0453595 (30 min, 10 ml/kg, 20% beta cyclodextrin, intraperitoneal) and the effects on novel object recognition and social interaction were evaluated.
Results: Muscarinic LTD is a form of synaptic plasticity essential for mPFC-mediated learning and memory. PCP-treated mice displayed significant deficits in CCh-induced mLTD in pyramidal neurons of the mPFC, an M1 receptor-mediated form of synaptic plasticity. However, other responses to M1 activation in mPFC pyramidal neurons remained unaltered after the PCP administration as no deficits were observed in CCh-induced increases in spontaneous EPSCs or CCh-induced inward current. In addition, profound mPFC-mediated cognitive deficits and negative symptoms¬ were observed in these mice following repeat PCP treatment. Interestingly, bath application of 10 microM VU0453595 reversed the mLTD deficits in the PCP-treated mice to levels similar to control mice. Moreover, VU0453595 demonstrated dose-dependent reversal of cognitive deficits in the novel object recognition task, as well as negative symptoms associated with social interaction in the chronic PCP mouse model of schizophrenia. Finally, VU0453595 does not cause any adverse effects observed with previous M1 agonists.
Conclusions: Utilizing the chronic PCP-treated mouse model, these studies demonstrate that selective potentiation of M1 can reverse not only deficits in mPFC neurotransmission but also negative symptoms and cognitive deficits and provide a novel therapeutic strategy for the treatment of schizophrenia. These results provide critical data in validating the potential utility of M1 PAMs as a novel therapeutic approach for treatment of negative and cognitive symptoms in schizophrenia patients.
Keywords: schizophrenia, cognition, negative symptoms, muscarinic acetylcholine receptor.
Disclosure: Dr. Rook's work has been funded by NIH. Dr. Daniels' work has been funded in part by the NIH and the Molecular Libraries Probe Production Centers Network. He has received compensation as a member of the scientific advisory board of the Sigma-Aldrich company and through consulting for Agios Pharmaceuticals Company and the Michael J. Fox Foundation. He is an inventor on patents that protect different classes of metabotropic glutamate and muscarinic receptor allosteric modulators. Dr. Lindsley's work has been funded by the NIH, Bristol-Myers Squibb, AstraZeneca, Michael J. Fox Foundation, as well as Seaside Therapeutics. He has consulted for AbbVie and received compensation. He is an inventor on patents that protect different classes of metabotropic glutamate and muscarinic receptor allosteric modulators. Dr. Conn has been funded by NIH, Johnson and Johnson, AstraZeneca, Bristol-Myers Squibb, Michael J. Fox Foundation, Seaside Therapeutics and Thome Alzheimer's Disease Drug Discovery Foundation. He has consulted over the past three years for Pfizer,

Cambridge and Millipore Corporation and received compensation. Over the past three years he has served on the Scientific Advisory Boards and received compensation from Seaside Therapeutics, Michael J. Fox Foundation, Stanley Center for Psychiatric Research Broad Institute (MIT/Harvard), Karuna Pharmaceuticals, Lieber Institute for Brain Development Johns Hopkins University, Clinical Mechanism (POCM) and Proof of Concept (POC) Consortium, and Neurobiology Foundation for Schizophrenia and Bipolar Disorder He is an inventor on patents that protect different classes of metabotropic glutamate and muscarinic receptor allosteric modulators.

W199. More than a Replacement Therapy: Amphetamine Treatment Reverses the Behavioral and Neurochemical Consequences of Cocaine Self-Administration

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Background: Cocaine abuse and dependence are major health problems with no FDA-approved pharmacotherapies. Cocaine addiction results in reduced dopamine system functioning and a reduced ability of cocaine to increase dopamine levels in reward-related brain regions. Long-access cocaine self-administration in rodents results in similar changes, characterized by reduced dopamine release and reduced potency of cocaine at the dopamine transporter (DAT). Therefore, an effort has been made to normalize these dopamine system deficits in order to ameliorate the neurochemical consequences of cocaine abuse that may drive cocaine addiction. Although amphetamine (AMPH) has been examined as a potential treatment for cocaine addiction, with promising behavioral results in rodents, monkeys and humans, the mechanism for AMPH-induced decreases in cocaine reinforcement has yet to be elucidated. It has been proposed that AMPH acts as an agonist replacement therapy; however, our data suggest that these effects may also be a result of AMPH-induced stabilization of the dopamine system.
Methods: Following acquisition of cocaine self-administration, animals were allowed to administer cocaine on a fixed-ratio 1 schedule of reinforcement (0.75 mg/kg, infused over 4 s) for six (long-access) or one (short-access) hours per day for a total of 14 days, with or without a 7-day abstinence period. Animals were treated with mini-pump delivered AMPH (5 mg/kg/day) or saline throughout the 14 days of self-administration or throughout abstinence. Escalation of cocaine intake has been suggested to model the dysregulated cocaine intake that occurs in cocaine addicts, thus we aimed to determine how an AMPH mini-pump alters this intake pattern. The reinforcing effects of cocaine have been shown to be dependent on its ability to inhibit the DAT and elevate accumbal dopamine levels, therefore, we used ex vivo fast scan cyclic voltammetry in brain slices containing the nucleus accumbens core to determine the ability of AMPH treatment to normalize cocaine-induced dopamine system dysfunction.
Results: We found that treatment with 5 mg/kg/day AMPH significantly attenuated escalation of cocaine intake, suggesting that AMPH treatment has a protective effect against the elevated cocaine consumption over time that is a characteristic of addiction. In regard to the effects of AMPH treatment on the dopamine system, we found that long-access reduced cocaine potency for dopamine uptake inhibition, and in line with the behavioral data, AMPH treatment blocked the development of cocaine tolerance when administered during cocaine self-administration. Providing more evidence that the effects of AMPH on cocaine intake are independent of agonist replacement, AMPH, when administered after cocaine self-administration, completely reversed cocaine tolerance. Further, in addition to cocaine effects at the DAT, AMPH treatment reversed deficits in basal dopamine signaling whereby both DA release and uptake were decreased by long-access cocaine self-administration and increased back to control levels by AMPH treatment.
Conclusions: Together, these data provide evidence that some effects of AMPH on cocaine intake are independent of agonist replacement therapy. We hypothesize that AMPH reduces cocaine self-administration, at least in part, by reversing the cocaine-induced alterations in the dopamine system. Although previous literature has shown promising behavioral results suggesting AMPH is a potentially effective treatment for cocaine abuse, this is, to our knowledge, the first investigation of the neurochemical mechanisms for these results. While agonist therapies for cocaine addiction are controversial and AMPH has a high abuse potential, these data may be able to define a mechanism for some of AMPH's therapeutic effects, which could drive the design of more targeted pharmacotherapies with less abuse liability.
Keywords: cocaine, voltammetry, nucleus accumbens, treatment.
Disclosure: Nothing to Disclose.

W200. Using the PDE4 Inhibitor ABI-4 to Quantify the Relationship Among in Vitro Potency, Ex Vivo Target Occupancy and in Vivo Efficacy

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Background: Inhibition of phosphodiesterase 4 (PDE4) has been the subject of a broad range of research efforts over the last 2 decades. Multiple compounds such as the prototypic PDE4 inhibitor, rolipram, have been profiled in preclinical models of inflammation, psychosis, cognition and depression. There are only 2 FDA-approved PDE4 inhibitors: roflumilast (Daxas®) for the treatment of chronic obstructive pulmonary disease (COPD) and apremilast (Otezla®) for psoriatic arthritis. To date, no PDE4 inhibitors have been approved for CNS indications. Here we present data demonstrating the potency of the novel brain penetrant PDE4 inhibitor, ABI-4 in models of psychosis and

inflammation and relate these to free drug concentrations, central target occupancy, and in vitro potency.
Methods: Adult male C57Bl/6 mice were used unless stated otherwise. For measurement of PDE4 occupancy, mice were dosed with ABI-4 (0.032-1 mg/kg s.c.), followed by [3H]rolipram (100 microCi/kg, intra-orbital). Percent displacement of rolipram binding in the prefrontal cortex was calculated to determine target occupancy. To assess potency for improving prepulse inhibition (PPI), mice were dosed with ABI-4 (0.032-1 mg/kg s.c.) and their startle response to an auditory tone, with or without prepulse, measured. To obtain a physiological measure of sensory processing, mice were implanted with skull screws above the frontal cortex. The EEG responses to pairs of auditory tones were recorded at baseline and after dosing with ABI-4 (0.01-1.0 mg/kg s.c.). The magnitudes of the auditory evoked potential (AEP) caused by the first and second stimuli were measured. To assess anti-inflammatory potency, male Lewis rats were given an intraplantar dose of lipopolysaccharide (LPS; 0.03 mg). Four hours later, rats were administered ABI-4 (0.01-0.3 mg/kg p.o.). Twenty six hours after systemic LPS, rats were euthanized and the aqueous humor removed for measurement of leucocyte infiltration. Effects of ABI-4 were compared to vehicle (25% PEG400, 75% (20% 2-hydroxypropyl-beta-cyclodextrin)) in all assays. All studies were reviewed and approved by the Institutional Animal Care and Use Committee at Pfizer. Plasma and brain concentrations of ABI-4 were determined using a liquid chromatography with mass spectral detection (LC-MS/MS) bioanalytical method. Plasma and brain binding were determined by equilibrium dialysis to allow for determination of unbound concentrations.
Results: ABI-4 (0.032 to 1 mg/kg) caused dose-dependent displacement of [3H]rolipram from prefrontal cortex with 50% displacement (ED50) calculated to occur at a dose of 0.06 mg/kg (unbound brain EC50 4 nM). ABI-4 improved sensorimotor gating as measured by an improvement in PPI with a minimum effective dose (MED) of 0.1 mg/kg (unbound brain concentration 2.5 nM). ABI-4 produced a dose dependent improvement in auditory gating, as indicated by a decrease in the ratio of the amplitude of the AEP in response to the second compared to the first stimulus (50% maximum reduction with unbound brain EC50 1.8 nM). ABI-4 produced potent anti-inflammatory effects measured by dose-dependent reduction in leucocyte infiltration of the aqueous humor in response to systemic LPS (unbound plasma IC50 0.7 nM).
Conclusions: These data demonstrate that ABI-4 binds with high potency to PDE4 in mouse brain. Fifty percent of rolipram binding was inhibited at a free brain exposure of 4 nM which is well aligned with the in vitro Ki (1.8 nM). Dose dependent improvements were seen in both the behavioral (PPI) and electrophysiological (EEG) measures of sensory processing. In both assays efficacy was observed at exposures expected to achieve $\geq$50% central target occupancy. ABI-4 also had potent effects in the endotoxin induced uveitis model of inflammation. Anti-inflammatory efficacy occurred at unbound plasma exposures $\geq$ 0.7 nM. Overall there was good agreement among in vitro potency, target occupancy and efficacy in preclinical models relevant to psychosis and inflammation.

Keywords: PDE4, sensory processing, inflammation, schizophrenia.
Disclosure: All authors are employees of Pfizer Inc.

W201. Antidepressant Properties of Silexan (Lavender oil): Activity in the Forced Swimming Test and Neurotrophic Effects via Creb Activation

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Background: In previous studies we could demonstrated that Silexan, an oral Lavender oil preparation, inhibits the opening of voltage dependent calcium channels (VOCCs) similar to the anxiolytic drug pregabalin. However, unlike pregabalin, Silexan is devoid of sedative properties in typical experiments. This was also supported by recent clinical studies indicating that Silexan exerts safe therapeutic effects in patients with general anxiety disorders and specifically in patients with subtreshold anxiety without having sedative side effects. In the latter population significant effects on the depression subscores were found, suggesting certain antidepressant properties which were subsequently confirmed in several preclinical experiments.
Methods: Neuritogenesis was determined in PC12 cells (rat) or SY5Y cells (human) after three days of incubation and CREB acrivation data are based on Western plot analysis of the phosphor-CREB vs. CREB ratio in PC12 cells. For the forced swimming test Wistar rat were used and immobility time was determined after 9 days of oral treatment.
Results: Silexan increased behavioral scores in the forced swimming test in vivo and stimulated neuritogenesis in PC12 cells and SY5Y cells in vitro. Such effects, typical for many antidepressant drugs, are generally linked to activation of the cAMP response element-binding protein (CREB). This could also be shown for Silexan in our recent experiments were stimulation of neuritogenesis was accompanied by increased levels of growth associated proteins and an increased ratio of P-CREB vs. CREB. Pregabalin was not active these experiments. We also identified the pathways involved in CREB' activation using different inhibitors of kinases being part of the cascade that finally leads to CREB phosphorylation. Our results show that kinases such as PKA, PI3K, MAPK and CaMK IV are clearly involved in the neurotrophic effects of Silexan.
Conclusions: In summary, beside potent anxiolytic properties, Silexan disposes of intrinsic antidepressant properties in contrast to pregabalin.
Keywords: lavender oil, neuritogenesis, CREP phosphorylation, forced swimming test.
Disclosure: WM (grant support and speakers fee Schwabe Pharmaceuticals), GS (none), CF (none), MN (fulltime emploee Schwabe Pharmaceuticals), AD (fulltime employee Schwabe Pharmaceuticals), SK (grant support and speakers fee Schwabe Pharmaceutical), KF (grant support Schwabe Pharmaceuticals).

W202. Class I Histone Deacetylase (HDAC) Inhibition Reduces the Mania-like Behavioral Phenotype of ClockΔ19 Mutant Mice

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Background: Emerging evidence implicates altered epigenetic and circadian rhythm mechanisms as putative contributors to the pathophysiology and the treatment of mood disorders, including bipolar disorder. Preclinical studies indicate that circadian genes, which form the transcriptional-translational feedback loops of the molecular clock, directly modulate mood-related neurocircuitry, and inhibiting the activity of specific HDACs may have therapeutic utility in the treatment of bipolar disorder and other psychiatric diseases. HDACs are enzymes capable of inducing long-lasting and relatively stable changes in gene transcription by removing acetyl groups from histone complexes. Valproic acid (VPA), a first line medication for bipolar disorder, is known to directly inhibit the enzymatic activity of both class I and IIa HDACs. However, it unclear whether valproic acid may exert its therapeutic effects via HDAC inhibition, and whether HDAC inhibition may have any therapeutic utility for bipolar disorder. Previously, we reported that a mouse carrying a mutation in one of the core transcription factors of the molecular clock, the ClockΔ19 mutant, displays a behavioral repertoire with high face validity to the primary clinical symptomology of bipolar mania (e.g., circadian disruptions, hyperactivity, reduced anxiety and depression, and hyperhedonia) that is reversed by chronic lithium treatment. In the present study, we investigated whether valproic acid and/or suberoylanilide hydroxamic acid (SAHA), a pan-HDAC inhibitor, normalized the anxiety and depression behavioral phenotypes in ClockΔ19 mutant mice. We then identified the specific class of HDACs that are involved in therapeutic effect using a combination of pharmacological, molecular, and viral-mediated gene knockdown approaches.
Methods: Male wild-type (WT) and ClockΔ19 mutant mice (n = 12-15 per group) were treated with appropriate vehicles, or VPA (chow), SAHA (drinking water, ~100mg/kg), MC1568 (i.p., 20mg/kg), or MS275 (mini-pump, 40mg/kg) for 12-14 days. Pharmacological inhibition of specific classes of HDACs were as follows: VPA, class I and IIa; SAHA, class I and IIb; MC1568, class IIa; and MS275, class I. Mice underwent behavioral testing during the last five days of pharmacological treatments, which consisted of the following assays: locomotor activity in a novel environment, open-field (OF), elevated plus maze (EPM), dark-light box (D/L box), and forced swim test (FST). To knockdown HDAC1 or HDAC2, WT and ClockΔ19 mutant mice (n = 6-15 per group) were injected with shRNA-HDAC1 or HDAC2-AAV2 (or Scramble, control) into the ventral tegmental area (VTA) or the ventricles (intracerebroventricular, ICV). Mice underwent similar behavioral tests as above. Brains were collected for gene, protein, and chromatin immunoprecipitation (ChIP) assays to investigate the effects of HDAC inhibitors on the expression of potential gene and protein targets, and epigenetic markers of gene transcription.
Results: Valproic acid, SAHA, and MS275, normalized the anxiety-related and depression-related behaviors in male ClockΔ19 mutant mice, except for MC1568, which resulted in a mixed behavioral state (i.e., selectively normalized depression-related behavior). As expected, valproic acid and SAHA increased global histone acetylation and differentially altered the expression of dopamine pathway genes in the VTA. To identify the specific class I HDAC that may be the primary target of these compounds, we knocked down HDAC1 and HDAC2 (both class I HDACs and previously noted for their effects on mood-related behaviors) in the VTA and ICV. Surprisingly, both HDAC1 and HDAC2 knockdown VTA and ICV reduced anxiety and depression behaviors in WT mice, while only HDAC2 knockdown both in the VTA and ICV normalized these behaviors in ClockΔ19 mutant mice.
Conclusions: Both valproic acid and SAHA normalized the mania-like behavioral phenotypes of ClockΔ19 mutant mice. Similar effects were found for MS275, suggesting targeting class I HDACs may be useful for the treatment of bipolar mania. Moreover, the therapeutic action of these compounds is likely mediated by targeted inhibition of HDAC2, a class I HDAC that has been associated with schizoaffective and bipolar disorders. These results begin to provide preclinical evidence for the potential of HDAC inhibitors as novel therapeutics for mood disorders. Future studies will further elucidate the molecular mechanisms and neurocircuitry involved in the therapeutic action. We also plan to use genome-wide high-throughput sequencing approaches to identify the pertinent, and potentially novel, gene networks involved in the behavioral effects of targeted class I HDAC inhibition. Financial support: IMHRO Johnson and Johnson Rising Star Award to MCCLUNG and NARSAD Young Investigator Grant to LOGAN.
Keywords: bipolar disorder, valproic acid, HDAC inhibitors, circadian rhythms.
Disclosure: Nothing to Disclose.

W203. The Development of Impulsive Choice is Primarily Mediated by Adrenergic 2A Receptors

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Background: Childhood impulsivity wanes into adulthood. Elevated levels of impulsivity are a symptom of attention deficit hyperactivity disorder (ADHD), other mental illnesses, and a risk factor for addiction. Impulsive choice behavior can be reduced with psychostimulants through increased monoamine activity within the prefrontal cortex (PFC) and its modulation on the nucleus accumbens (NAc). However, we have recently shown that over-expression of the dopamine D1 receptor on PFC afferents increases impulsive choice in adult animals. Moreover, D1 receptors are elevated during adolescence on PFC projections to the NAc, which may explain elevated levels of impulsivity during adolescence. In addition, noradrenergic Alpha-2A receptor activity reduces impulsivity, but we do not know

if similar transient changes occur on the specific population of glutamatergic projection neurons. Together, these observations raise the question of whether impulsive choice is modulated by a balance between D1 and Alpha-2A receptors. Little is known about the development of the neurobiological underpinnings of either of these receptor systems and their co-localization within the PFC. In order to better understand the development of these basic mechanisms and the behavioral consequences of their manipulation, we conducted the following study.

Methods: Sprague-Dawley male rats that were juveniles (postnatal day [P] 27), adolescents (P44), and adults (P90) were used. Three different groups of subjects were used for three different experiments: 1) assessment of delay discounting in typically-developing subjects; 2) characterization of the normative development of D1 and Alpha-2A receptors within medial PFC (mPFC) projections to the NAc; and 3) manipulation of D1 and Alpha-2A expression with glutamate-specific lentiviral vectors to determine the causal role of these receptors to alter impulsive choice. A t-maze test of delayed discounting was used, where subjects chose between a smaller reward sooner or a larger reward after a 5, 10, or 15 sec delay. Retrograde fluorescent beads were microinjected into the NAc and tissue was immunologically stained for Alpha-2A and D1 receptors. Lastly, lentiviral vectors that express GFP, D1, or Alpha-2A on glutamatergic neurons were microinjected into the mPFC.

Results: Impulsive choice was significantly higher in juveniles at the short delay of 5 sec, but adolescents significantly differed from the other ages at the 10 and 15 sec delay ($F4,57 = 4.44$, $p = 0.01$). Significant differences were evident on the normative assessment of D1 and Alpha-2A receptors and their co-localization when specifically focused on projection neurons between the mPFC $\Rightarrow$ NAc (D1: $F2,60 = 22.3$, $p < 0.001$; Alpha-2A: $F2,30 = 5.58$, $p < 0.01$). D1 was transiently higher during adolescence relative to the other ages, whereas Alpha-2A had a linear increasing pattern across development. Neither differences in co-localized receptor expression nor expression differences between layers 2/3 and 5/6 were significant. Lentiviral vectors were used to determine experimentally which of these two receptors may greatly influence impulsive choice. Over-expression of D1 receptors increased impulsive choice at the 5 sec delay in adults, with little effect at other ages ($F2,62 = 3.50$, $p < 0.05$). In contrast, Alpha-2A receptor over-expression significantly reduced impulsive choice in the juveniles at all delays ($F2,63 = 5.83$, $p < 0.01$), with no effect in adolescents and opposite effects in adults.

Conclusions: Impulsive choice reflects a balance between D1 and Alpha-2A receptors in the mPFC. Under conditions where expression of both receptor types is low (juveniles), impulsive choice is elevated and can be reduced by presumed increased activity of Alpha-2A receptors. Adolescent impulsive choice is higher at later delays, as Alpha-2A is still sufficiently low, but D1 expression is high. Given the rather "balanced" distribution of these receptors, impulsive choice is difficult to modulate with viral vectors. In adulthood, the typical expression of Alpha-2A is sufficiently elevated such that D1 over-expression increases impulsivity only at the 5 sec delay. These data partially support the imbalance hypothesis of adolescent risk proposed by Casey, which states that adolescent risky behaviors occur because the reward system is more active than the executive control systems. Our data bias this hypothesis in the other direction: an immature control system plays a more fundamental role in the expression of impulsive choice.

Keywords: impulsivity, delayed discounting, gunaficine, ADHD.

Disclosure: Nothing to Disclose.

W204. Pituitary Adenylate Cyclase-activating Polypeptide Regulates Excessive Alcohol Consumption

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Background: The etiology of alcoholism is complex: heritable susceptibility factors interact with environmental factors to produce the disease. The neurobiological mechanisms mediating the propensity to consume excessive amounts of alcohol are still not well understood.

Methods: Using genetically selected alcohol-preferring rats, a well-established animal model of alcoholism, we here demonstrate that central administration of a peptide antagonist for the pituitary adenylate cyclase-activating polypeptide receptor 1 (PAC1), the cognate receptor for the neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP), blocks excessive alcohol drinking as well as motivation to drink in alcohol-preferring rats. On the other hand, the PAC1 antagonist did not significantly affect water, saccharin intake, or responding for ethanol in non-selected Wistar rats. In addition, the antagonist significantly reduced responding maintained by alcohol-associated incentive stimuli (seeking behavior).

Results: Using immunohistochemistry, a significant reduction in the number of PAC1 positive cells was observed selectively in the Nucleus Accumbens (NAcc) Core of alcohol-preferring, compared to Wistar rats. Proving the functional relevance of these changes, excessive drinking in alcohol-preferring rats was markedly reduced by microinfusion of the PAC1 antagonist into the Core, but not the Shell, of the NAcc. Finally, using retrograde tracing techniques coupled with immunofluorescence, we show that the dopaminergic neurons of the VTA which project to the NAcc core co-express the neuropeptide PACAP.

Conclusions: Altogether our findings demonstrate that the dysregulation of the PACAP/PAC1R system, specifically in the NAcc core, promotes excessive drinking and alcohol-seeking behavior, indicating that blockade of the PACAP/PAC1R system may represent a novel target for alcohol addiction.

Keywords: Ethanol, Preferring, Self-Administration, Addiction.

Disclosure: Nothing to Disclose.

W205. Adolescent Corticosterone Exposure Alters Regulation of alpha2a-Adrenergic Receptor Sensitivity: Possible Role in Stress-induced Motivation for Alcohol

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Background: High levels of stress during different phases of development, including adolescence, is associated with an increased risk for the development of a variety of neuropsychiatric disorders, including anxiety and substance use disorders. Several studies have demonstrated that many of the effects of chronic stress are mediated by glucocorticoid receptor signaling. Therefore, chronic elevation of glucocorticoids may produce long-lasting changes in brain function that increases risk for psychiatric disorders, and determining the molecular consequences of glucocorticoid exposure in the brain may help identify novel therapeutic targets.
Methods: Adolescent male rats were exposed to the primary glucocorticoid hormone in rodents, corticosterone (CORT), via their drinking water for 20 days (PND 30-50) and were then maintained on normal tap water for the duration of the experiments. Controls were given normal tap water throughout. Rats were then divided into groups that were trained to self-administer 10% ethanol + 0.1% saccharin or 20% sucrose beginning on PND 60. Rats had 20 days of self-administration training and underwent reinstatement testing. Rats were left undisturbed for another week and were then euthanized by focused microwave irradiation and their brains dissected. The amygdala of these animals was analyzed by quantitative label-free mass spectrometry to identify proteins differentially phosphorylated by prior adolescent CORT exposure, ethanol self-administration and their interaction. One differentially phosphorylated protein, the alpha 2A adrenergic receptor (a2AR) was examined further in behavioral studies to determine if modulation of a2AR phosphorylation by inhibition of the G-protein receptor coupled kinase 2 (GRK2) could alter motivation for and reinstatement to ethanol seeking induced by the pharmacological stressor yohimbine.
Results: Prior adolescent CORT exposure increased maintenance levels of self-administration of ethanol + saccharin but not sucrose. The phosphorylation profile of proteins in the amygdala was significantly altered by prior adolescent CORT exposure, while there were no interactions between adolescent CORT exposure and the reinforcer self-administered. Thus, when the ethanol and sucrose groups were collapsed, principle components analysis revealed distinct phosphorylation profiles between adolescent CORT and H2O exposed groups. One phosphopeptide that was significantly increased by adolescent CORT was phosphorylation of the a2AR on serines 296-299. Phosphorylation at these sites is mediated by GRK2, thus, we then tested the effect of a GRK2 inhibitor infused into the basolateral amygdala (BLA) on yohimbine-induced progressive ratio (PR) responding and reinstatement to ethanol seeking. We found that intra-BLA GRK2 inhibition significantly reduced yohimbine-induced increases in PR responding and reinstatement to ethanol seeking in both adolescent CORT treated and control rats.
Conclusions: The results of these studies indicate that adolescent exposure to CORT can cause significant changes to the amygdala phosphoproteome that persists into adulthood and that changes in a2AR desensitization induced by GRK2 may mediate some behavioral differences observed in adolescent CORT treated animals. Moreover, GRK2 inhibition may represent a novel target for reducing anxiety and stress-induced alcohol drinking and relapse.
Keywords: alcohol, adolescence, corticosterone, adrenergic receptor.
Disclosure: Nothing to Disclose.

W206. Both Lurasidone and Fluoxetine Exerts Antidepressant-like Effects on Novelty-induced Hypophagia and Reduce NMDA Receptor Subunits along with PSD-95 in Mice Hippocampus and Frontal Cortex

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Background: Lurasidone is a second generation antipsychotic drug which is approved for the treatment of schizophrenia, but also against depressive episodes associated with bipolar type I disorder. Lurasidone acts as a high affinity antagonist at multiple receptors, particularly 5-HT2A, 5-HT7, D2 and α2 receptors, and as a partial agonist at 5-HT1A receptors. Over the past years, it has been convincingly demonstrated that NMDA receptor antagonism has antidepressive effects. There is also accumulating evidence that chronic treatment with monoaminergic antidepressants exert therapeutic actions by altering glutamate receptor-mediated neurotransmission. Here, we studied the behavioral responses of chronic oral administration with lurasidone (3 or 10 mg/kg), fluoxetine (20 mg/kg) or saline in the novel-induced hypophagia (NIH) test and the regulation of NMDA receptor subunits and related proteins.
Methods: Adult male C57Bl/6J mice were used. All experiments were carried out in agreement with the European Council Directive (86/609/EEC) and were approved by the local Animal Ethics Committee (Approval number N40/13; Stockholms Norra Djurförsöksetiska Nämnd). Mice were randomly assigned to one of four treatment groups (n = 10 per group): Vehicle (i.e. 0.5% methyl cellulose); lurasidone, 3 or 10; or fluoxetine, 20mg/kg. All drugs were once administered daily, per os (p.o.), using disposable gavage needles at a volume of 10ml/kg body weight. Animals received daily treatment for three weeks before subjected to three consecutive days of training for the NIH test in which they were, during 15 minutes, presented in their home cage with diluted sweetened condensed milk. On day four, the latency from bottle presentation to first milk-licking event in the home cage, was manually scored by an observer. On day five, the same test was performed under aversive conditions (in novel cages, lacking bedding and under bright illumination). The NIH was measured by the latency to drink the sweetend

milk under these aversive conditions. Three days after the NIH test, mice were killed by cervical dislocation and decapitation and brain regions immediately dissected out and frozen at -80oC. The collected tissue from hippocampal and prefrontal cortices was sonicated and boiled. Equal amounts of protein were loaded and separated by SDS-PAGE, transferred to PVDF membranes and immunobloted with specific antisera against β-Actin, Synapsin I, Spinophilin, PSD-95, NA2A, NA2B, NA1 and GluA1. After incubation with the polyclonal HRP–conjugated secondary antibody, immunoreactivite bands were detected by enhanced chemiluminescence and quantified by densitometry with the NIH Image J 1.40 software.

Results: Vehicle, lurasidone at 3 and 10 mg/kg and fluoxetine was tested in the NIH test. Repeated measures ANOVA of latencies indicated an effect of novel cage environment ($F1,24 = 66$; $p < 0.001$) and novel cage environment x treatment interaction ($F3,24 = 5,77$; $p < 0.001$). Post-hoc analysis demonstrated that both doses of lurasidone ($p < 0.05$), as well as fluoxetine ($p < 0.001$), significantly lowered latency to sweetened milk consumption when compared to vehicle. Immunoblotting data from hippocampus was analyzed with one-way ANOVAs and showed treatment effects on NMDAR subunit levels (NA1 ($F3,32 = 2,98$; $p < 0.05$); NA2A ($F3,31 = 4,19$; $p < 0.05$)) and PSD-95 ($F3,32 = 3,79$; $p < 0.05$)). Post-hoc analyses showed significant reductions of these proteins by lurasidone (10 mg/kg) and fluoxetine when compared to saline. Likewise, immunoblotting data from the frontal cortex demonstrated treatment effects on NMDAR subunit levels (NA1 ($F3,33 = 2,88$; $p < 0.05$); NA2A ($F3,30 = 12,42$; $p < 0.001$); NA2B ($F3,32 = 4,66$; $p < 0.01$)) and PSD-95 ($F3,32 = 5,23$; $p < 0.01$). Post-hoc analyses showed significant reductions of these proteins by lurasidone (10 mg/kg) and fluoxetine when compared to saline. Post-hoc analyses showed that both doses of lurasidone and fluoxetine significantly decreased NA2A. Lurasidone (10 mg/kg) and fluoxetine significantly decreased NA2B subunits and PSD-95. Only fluoxetine reduced NA1 subunits in this region.

Conclusions: These data indicate that antidepressive effects of lurasidone, as well as fluoxetine, could involve reduced NMDA receptor-mediated signal transduction, particularly in pathways regulated by PSD-95, in hippocampus and frontal cortex.

Keywords: lurasidone, NMDA receptors.
Disclosure: This study was supported by Swedish Reseach Council (PS), Dainippon Sumitomo (PS) and the European Union Seventh Framework Program, under grant agreement FP7-People-ITN- 2008-238055 ("BrainTrain" project) (TS).

W207. Oxytocin-driven Endocannabinoid Regulation of Sociability

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Background: Sociality is a hallmark of human behavior and is essential to health and group survival. Nevertheless, the neural systems that underlie the expression of social behavior and encode for the reward of social interactions remain largely unknown. Clues indicate that the endogenous cannabinoid ('endocannabinoid') system might be involved: (a) users of marijuana, a drug that hijacks this system, report changes in sociability, and (b) endocannabinoids regulate mood and cognition through the activation of type-1 cannabinoid (CB1) receptors, which are richly expressed in areas of the brain involved in social behavior. However, how the endocannabinoids system might regulate sociability and its possible dysregulation in social impairment is unknown.

Methods: We used two distinct tests of social behavior. In the social reward test, mice were conditioned for 24 h to one type of bedding with cage-mates (social), then 24 h to another bedding alone (isolated). Place preference for the bedding on which mice were socialized is indicative of social reward. In the social approach test mice were exposed to a three-chambered apparatus and given the choice between a chamber with a novel mouse or a chamber with an object. Liquid chromatography-mass spectrometry was used to measure endocannabinoid and endocannabinoid-related lipids in the brain.

Results: We find that oxytocin, a neuropeptide crucially involved in social behavior, drives the production of the endocannabinoid anandamide during social stimulation. To assess the functional significance of this interaction, we used a model of enhanced anandamide signaling in which the anandamide-deactivating enzyme, fatty acid amide hydrolase (FAAH), is deleted through homologous recombination. Oxytocin receptor blockade prevents social reward in wild-type but not FAAH-null mice. We extend these findings to a model of social impairment, in which restoration of a deficient oxytocin-driven anandamide signal corrects the social impairment in a cannabinoid type-I (CB1) receptor-dependent manner. Together, these findings suggest that an oxytocin-driven anandamide signal regulates sociability in mice.

Conclusions: A novel interaction between oxytocin and anandamide provides important implications for the understanding of sociability and social impairment, a cardinal feature of many neuropsychiatric disorders.

Keywords: endocannabinoid, oxytocin, sociability.
Disclosure: Nothing to Disclose.

W208. Bridging the Gap Between alpha-7 Receptor Priming and Cognitive Enhancement in the Clinic and in Pre-clinical Animal Models

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Background: Cognitive impairment is a central deficit in many neurological and psychiatric disorders. Currently, several pro-cognitive therapies are under development, including agonists of the alpha-7 nicotinic acetylcholine receptor. Alpha-7 receptors are located in brain areas involved in various domains of cognition, including attention, executive functioning, and long-term and work-

ing memory. We have demonstrated that encenicline, a novel, potent alpha-7 partial agonist, activates the alpha-7 receptor by itself at concentrations that are several-fold higher (EC50 = 150-390 nM) than the equilibrium binding constant (Ki = 10 nM) for this receptor and also has physiological activity at alpha-7 receptors at concentrations below the Ki in the presence of acetylcholine (0.3 nM). The latter activity at low concentrations is consistent with the range of unbound plasma concentrations that demonstrated activity in clinical studies and in pre-clinical animal models of cognition. We have termed this phenomenon priming, because this mechanism appears to require the presence of the natural ligand, acetylcholine. We now present new data addressing how alpha-7 agonists affect hippocampal neuronal networks involved in cognition at priming concentrations.

Methods: Close analogs of encenicline (FRM-0017848 and FRM-0017874), with similar activities at alpha-7 receptors were used in these experiments. The analogs were tested for priming activity in Xenopus oocytes using 40-μM, intermittent applications of acetylcholine and bath application of the analogs. In the hippocampus, alpha-7 receptors are localized primarily on GABAergic interneurons and we conducted studies to determine the effects of alpha-7 receptor activation on local circuit activity. GABAergic IPSCs and glutamatergic EPSCs were measured in rat hippocampal slices in whole-cell patch-clamp recordings of pyramidal neurons. Long-term potentiation (LTP), a physiological correlate of cognition, was generated by theta burst stimulation of the Schaffer collaterals in angled rat septo-hippocampal slices that maintained the cholinergic input. Hippocampal theta rhythms, another physiological correlate of cognition, require activation of GABAergic interneurons and are enhanced by acetylcholine. Hippocampal theta rhythms, generated by stimulation of the nucleus pontis oralis (nPO), were recorded in urethane-anesthetized mice and rats. Independent pharmacokinetic studies were performed in both species for PKPD modeling. Cognition was tested in rats using a natural forgetting test (48-hour interval between trial 1 and 2) in a novel object recognition task and in mice using a water T-maze task with acquisition and reversal learning phases.

Results: FRM-0017848 demonstrated a rat alpha-7 receptor binding Ki of 9 nM and potentiated human alpha-7 receptors in Xenopus oocytes at 0.3 nM. At 3.16 nM FRM-0017848, GABAergic activity (normalized IPSC frequency) on hippocampal slice pyramidal neurons was 154% of control ($p = 0.013$). The resting membrane potential of glutamatergic pyramidal neurons was hyperpolarized ($p = 0.017$) and the number of spontaneous EPSCs was reduced by 3.16 nM FRM-0017848. These effects were blocked by the alpha-7 receptor antagonist methyllycaconitine (MLA, 50 nM). LTP (field EPSP amplitude) was also enhanced by 3.16 nM FRM-0017848 in rat septo-hippocampal slices by 12% ($p = 0.033$). FRM-0017848 at 1, 5.6, 10, and 31.6 nM did not enhance LTP. Donepezil at 500 nM increased LTP by a similar amount as 3.16 nM FRM-0017848. FRM-0017874 was used in in vivo experiments and had a rat alpha-7 receptor binding Ki of 18 nM and potentiated human alpha-7 receptors at 0.2 nM. Theta rhythm power, generated by stimulation of the nPO, was enhanced by on average about 40% beginning 15 minutes after dosing in C56Bl/6 mice at 1 and 3 mg/kg, sc ($p < 0.01$) and in Wistar rats at 0.3 and 1 mg/kg ($p < 0.02$). Lower and higher doses were not efficacious and theta frequency was not altered. Application of a PKPD model to these data described an inverted U-shaped dose-response effect function, with peak efficacious unbound brain concentrations in the theta rhythm studies of 1-6 nM. In the rat novel object recognition task, FRM-0017874 improved memory at 0.03, 0.1, and 0.3 mg/kg, sc when administered 30 minutes before trial 1 and at 0.3, 1, and 3 mg/kg, sc before trial 2 ($p < 0.05$). In the mouse water T-maze task, 3 mg/kg FRM-0017874 improved acquisition on day 4 and 1 and 3 mg/kg improved reversal learning on day 5 ($p < 0.05$).

Conclusions: These data demonstrate that the physiological correlates of cognition are enhanced by priming concentrations of alpha-7 agonists and provide a network level link between the priming activity at the receptor level and the observed effects on cognition in animals and humans at plasma concentrations below the Ki. These observations are in agreement with the clinically observed activities of encenicline at low doses in Alzheimer's disease and cognitive impairments for schizophrenia and have implications for additional disease states.

Keywords: alpha-7 nicotinic acetylcholine receptor, partial agonist, priming, electrophysiology.

Disclosure: : Gerhard Koenig, Matthew Townsend, Liza Leventhal, Cuyue Tang, Raymond Hurst, Timothy Piser, Ting Chen, Dana Hilt, and Dorothy Flood received compensation as employees from FORUM Pharmaceuticals Inc. Milan Stoiljkovic and Mihaly Hajos received compensation from FORUM Pharmaceuticals Inc. for conducting some of the studies.

W209. Strain-selective Effects of Kappa Opioid Antagonism, Buprenorphine's Potential as a Novel Antidepressant Compound

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Background: The prevalence of major depressive disorder and the limited efficacy of conventional antidepressants necessitate development of novel therapeutics for individuals with treatment resistant forms of depression. One promising target for antidepressant development is modulation of opioid receptors, specifically kappa opioid receptors (κ-ORs). Activation of κ-ORs by agonists such as the endogenous ligand dynorphin is known to regulate aversion and to induce depressive behaviors in rodents and humans. The primary goal of these studies was to ascertain whether buprenorphine (BPN), a medically available drug with mixed effects at opioid receptors, was effective in the Wistar Kyoto (WKY) rat strain, a rodent model of depression that demonstrates resistance to the behavioral effects of many antidepressants.

Methods: The antidepressant-like and anxiolytic-like effects of BPN were assessed in the forced swim test (FST) and the emergence test (ET) respectively, in the depressive-like WKY strain ($n = 8$ per group), and the outbred normosensitive Wistar ($n = 8$ per group) and Sprague Dawley (SD,

n = 6 per group) rat strains. BPN was administered once (0.25, 0.75 and 2.25 mg/kg s.c.) 24 h prior to behavioral testing. All procedures were carried out in accordance the National Institutes of Health Guide for the Care and Use of Laboratory Animals.
Results: Baseline behavior in the FST for all parameters differed between strains, WKY rats showed higher immobility and lower levels of climbing behavior than the other strains. BPN dose-dependently reduced immobility ($F3,27 = 3.71$, $p = 0.024$) and increased swimming behavior ($F3,27 = 3.03$, $p = 0.046$) in WKY rats only. Post-hoc tests revealed that the BPN induced significant behavioral effects at 0.75 mg/kg ($p < 0.05$) and 2.25 mg/kg ($p < 0.05$). In the emergence test, WKY rats exhibited significantly higher latencies to exit a protective tube than either SD or Wistar rats. A significant drug*strain interaction ($F2,74 = 2.60$, $p < 0.024$) was measured for emergence latency, where BPN reduced emergence latencies for WKY but not for SD or Wistar rats at 0.75 mg/kg ($p < 0.001$) and the 2.25 mg/kg ($p < 0.001$) dose.
Conclusions: These results indicate a striking selectivity for the behavioral effects of BPN in different strains of rats. Furthermore, these data support the utility of WKY rats as a genetic model of depression for measuring the effects of novel compounds on behaviors related to mood and anxiety. WKY rats exhibit substantially higher levels of κ-ORs in corticolimbic structures compared to normally behaved rodents, such as the Wistar and SD strains. The elevated κ-OR/dynorphin signaling of WKY rats may underlie both the depressive-like phenotype of the strain and their responsiveness to the behavioral effects of κ-OR antagonists, such as BPN. Additional studies are being conducted to address the impact of κ-ORs modulation of drug sensitivity and to evaluate the mechanisms underlying the antidepressant effects of BPN.
Keywords: Depression, Anxiety, Wistar-Kyoto, Buprenorphine.
Disclosure: Nothing to Disclose.

W210. Effect of Acute Administration of Agomelatine on the Memory Processes Triggered by Threat Responses to an Auditory Stimulus in Rats

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Background: Alterations in learning processes induced by the response to a threat (threat or fear learning) may be implicated in mood disorders. This particular kind of learning has been investigated with Pavlovian threat conditioning paradigms, consisting of pairing a neutral conditioned stimulus (CS), such as a tone, with an aversive unconditioned stimulus (US), such as a footshock. Upon subsequent exposure, the CS provokes a defense response. The novel antidepressant Agomelatine is a melatonergic receptor agonist and a 5-HT2C receptor antagonist. Its antidepressant/anxiolytic action has been extendedly demonstrated both in preclinical and clinical studies (1,2). Here we evaluate in rats how acute Agomelatine treatment might alter threat conditioning as well as its mechanism of action.
Methods: During training rats were exposed to two pairings of a 20-sec tone CS (5 kHz, 75 dB) that co-terminated with a footshock US (0.5 sec, 0.7 mA). Treatments were given acutely i.p. or intra-amygdala 2 hours before dark onset. The drug was administered at different memory stages: 30 minutes before training, immediately after training, or before memory testing. All drugs were dissolved in hydroxyethylcellulose 1%. Rats given pre or post-training administrations were tested for short-term memory 3 hours after conditioning with presentations of 3 unreinforced CSs. They were then tested 24 hours later for a long-term memory with 10 unreinforced CS presentations. Rats given pre-memory testing injections were tested 24 hours after training with 1) 10 unreinforced CSs (LTM test) or 2) with 20 unreinforced CSs (extinction training). The animals in the extinction experiment were subjected to a long-term memory extinction testing (5 unreinforced CSs) 24 hours after extinction training.
Results: A single pre-training injection of Agomelatine (40 mg/kg) significantly reduced freezing to the CS 24 hours after training but not during training or 3 hours after training. A single post-training or pre-testing injection of Agomelatine had no effect on conditioned threat memory expression. This pattern of results is consistent with an Agomelatine effect on the consolidation of threat-triggered memory. Agomelatine did not affect memory extinction training induced by the presentation of 20 CSs. Importantly, the animals that received Agomelatine before extinction showed significantly less spontaneous recovery of threat-triggered memory than control animals when tested 24 hours after extinction training. In order to characterize the mechanism of action of Agomelatine in the consolidation of threat memory, a pre-training injection of melatonin (40 mg/kg) or the 5-HT2C antagonist, S32006, (10 mg/kg) was administered. Neither of the drugs had any effect in memory consolidation suggesting that the synergy between both, melatonergic agonism and 5-HT2C antagonism, is necessary for this effect. In contrast an injection of S22153 (20 mg/kg.), a melatonergic antagonist, before the pre-training administration of Agomelatine, prevented the decrease in the consolidation of fear induced by the drug showing a role of the melatonin receptors on the effect of Agomelatine. Importantly, Agomelatine infused intra-cerebrally into the lateral amygdala before training induced a reduction in the consolidation of threat memory demonstrating that lateral amygdala is involved in the systemic effect of Agomelatine. In conclusion, Agomelatine acutely reduces memory consolidation in a rat model of auditory threat conditioning. Furthermore, Agomelatine constrains the initial return of threat-triggered memory after extinction training.
Conclusions: Interestingly, classical SSRIs have the same effects in memory consolidation as Agomelatine but only after 3 weeks of treatment (3). SSRIs have no effect (Fluoxetine, 4) or even impair the acquisition of extinction (Citalopram, 5). By contrast the SNRI Venlafaxine, with faster onset of therapeutic action and superior efficacy than SSRIs, causes the same effect in the consolidation of extinction (6) induced by Agomelatine. As regards to the pharmacological profile of Agomelatine, the present results suggest that a synergy between melatonergic agonist and 5-HT2C antagonist properties is necessary for the observed

reduction in consolidation of aversive memories. This result agrees with previous reports showing the necessity of the Agomelatine's joint activation of both receptors for alleviating depression in animal models (7). These results open a potential new therapeutic use of Agomelatine in order to prevent the development of pathological memories related to trauma and also to achieve a better outcome of psychological therapies based in extinction learning.
Keywords: Agomelatine, Threat Conditioning, Traumatic Memories, Memory Consolidation and Extinction.
Disclosure: This study has been funded by Servier Laboratories. E. Mocaër, C. Gabriel, and L. Seguin are employed by Servier Laboratories.

W211. Novel D-Amino Acid Oxidase Inhibitors

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Background: The legendary biochemist, Sir Hans Adolf Krebs discovered D-amino acid deaminase. Its main substrate, D-serine is a critically important co-agonist of the N-methyl-D-aspartate receptor (NMDAR). We recently demonstrated that sodium benzoate, as a D-amino acid oxidase (DAAO) competitive antagonist, can substantially improve the symptoms and neurocognition of schizophrenia, presumably enhance NMDA function by raising D-serine level. In mild cognitive impairment, sodium benzoate also improves the cognition and function. In retrospect, the history of glutamatergic treatments, developed in the past two to three decades, follow a similar path of the development of aminergic and GABAergic treatments. All three lines of treatments involve neurotransmitter and its precursor (chloroziapoxide, tryptophan), agonist/antagonist (L-dopa, chlopromazine), uptake blocker (imipramine, fluoxetine, bupropion), as well as catabolism inhibitor (iproniazid, selegiline). In analogy to the aminergic and GABAergic treatments, after the initial discovery of the therapeutic use of the co-agonists/partial agonists, including glycine, D-serine, D-cycloserine and D-alanine, the missing NMDA treatment options were obvious in the hindsight; first, the neurotransmitter uptake inhibition by glycine transporter-1 (GlyT-1) inhibitor; second, NMDAR antagonists; third, the inhibition of the DAAO. The treatment of DAAO inhibition is analogous to monoamin oxidase inhibitors (MAOI), which upregulates monoamine for CNS disorders like depression and Parkinson disease. In another word, DAAO inhibitors are similar to MAOI in raising the tone of neurotransmitter of interest, by inhibiting the catabolism enzyme.
Methods: In searching for candidate drugs that can safely activate NMDAR, we had screened and identified several DAAO inhibitors that can be potential therapeutics for CNS disorders. For DAAO activity assay, recombinant DAO-6Histidines (400 nM) was added into 3% (w/v) o-phenylenediamine, 1 U horseradish peroxidase, 40 mM D-alanine with a final volume of 200 μL. The reaction at 25 °C generated hydrogen peroxide that was oxidized by the peroxidase and further converted, in the presence of o-phenylenediamine, to 2,3-diaminophenazine, which was quantified by measuring OD450. For the inhibitor assay, candidate drugs at mM-nM was applied to determine the IC50. To confirm the findings of the enzyme assay, we also perform molecular docking study of the potential DAAO inhibitors. To decide the candidate for new drug development, we test the compounds with low IC50, which were confirmed by docking study, by animal behavior studies relevant to CNS disorders.
Results: We had identified more than 10 candidate DAAO inhibitors. To confirm the findings of enzyme assay, we also performed molecular docking study of the potential DAAO inhibitors, which confirm the findings in DAAO assay in large. One of the DAAO inhibitors, SND21, was confirmed to be a partial antagonist of DAAO, with ~75% inhibition the highest and IC50 at 24 μM, which is more potent than sodium benzoate (IC50 = 61μM). Its safety profile is satisfactory with NOAEL at ~150 mg/Kg in most toxicology studies. In animal models, it improves the acoustic pre pulse inhibition and attenuate the locomotion, while it does not affect the performance on elevated plus maze.
Conclusions: Given its activities in both the DAAO and rodent behavior assays, SND21 is chosen for the clinical development. It partial antagonism of DAAO activity is novel and may represent a safe approach not to over-activate NMDAR-mediate neurotransmission, while improving the symptoms of CNS disorders.
Keywords: NMDA, D-amino acid oxidase, D-serine, screening.
Disclosure: The study is supported by SyneuRx Internation Corp. where Dr. Tsai is a board director.

W212. Time Course of Oxytocin's Therapeutic-like Brain Effects

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Background: The neurohormone oxytocin (OT) has been proposed as putative therapeutic for a number of psychiatric disorders based on preclinical findings in animals and humans. This notion has only recently begun to be put to test using randomized clinical trials in patients with the proposed indications.However several critical gaps in our knowledge about OT present a barrier to designing optimal clinical trials to test OT's efficacy. For example, while it is generally assumed that intranasal administration is superior to other routes of administration in delivering OT to the brain, this has not yet been proven. Another unknown is the optimal daily dose of OT to treat the various psychiatric illnesses. Moreover, it is also not clear what is the optimal dosing schedule to produce the best therapeutic effects on the brain. Recently it has been demonstrated that both intransally and peripherally administered OT produce a rapid, but transient, increase in brain OT levels in rats and mice lasting less than 90 minutes after dosing. This brain pharmacokinetic data has potential implications for developing OT as treatment for psychiatric disorders. However, to date, the time course OT's brain pharmacodynamic effects have not been well characterized. Peripherally administered OT is known to increase prepulse inhibition (PPI) in the PPI-deficient Brown Norway rat. PPI is mediated by a well characterized brain circuit and

PPI enhancement in animals is considered predictive of therapeutic efficacy for schizophrenia and other neuropsychiatric disorders. We investigated the time course of intranasally and peripherally administered OT's PPI enhancing effects.
Methods: Doses of oxytocin or vehicle were administered subcutaneously or intranasally in adult male and female Brown Norway rats. Rats were tested in startle chambers at various intervals ranging from 30 minutes to 4 hours after OT administration. Each rat was tested only one time. PPI was measured using acoustic startling and prepulse stimuli.
Results: Subcutaneously administered OT increased PPI in both male and female Brown Norway rats at 30 and 60 minutes post administration but not at 90 minutes or subsequent times. Intranasal OT increased PPI only at 30 minutes post administration but not at 60 minutes or subsequent time points. Lower doses of OT were effective in facilitating PPI when administered intranasally compared to subcutaneously (0.14 mg/kg vs. 1 mg/kg).
Conclusions: These results suggest the brain pharmacodynamics of peripherally and intranasally administered OT are rapid but short-lived, a finding generally consistent with the brain PK effects recently reported. These results have implications for developing OT as a treatment for brain disorders, suggesting that more frequent dosing or extended release delivery systems may be required to maintain therapeutic effects on the brain. The fact that PPI enhancement was more sensitive to OT administered intranasally than peripherally, indirectly supports the notion that there is more efficient brain uptake of OT via the intranasal route.
Keywords: Oxytocin.
Disclosure: DF is named inventor of a patent filing involving oxytocin. DF has received research funding from Retrophin and Ferring. DF has received payment from Amneal for expert consulting.

W213. ASP0777: NMDA Channel Blocker with the Equal Subtype Selectivity and the Fast-Off Rate Has Potential as a Rapid Onset Antidepressant without Psychotomimetic Adverse Effects

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Background: Although there has been growing interest in the observation that ketamine has a rapid positive effect on depressive symptoms, the psychotomimetic properties limit its clinical use. Many attempts have been made to differentiate the underlying mechanisms of the efficacy and the adverse events. ASP0777 is a NMDA channel antagonist discovered by Astellas, and has been extensively profiled with 6 clinical trials involving 291 subjects up to 6 weeks treatments. The adverse events found in clinical trials were generally mild, CNS related (dizziness, headache, feeling abnormal), and dose dependent. Here we show that ASP0777 is NMDA channel blocker with fast-off rate, and is equally selective to the four subtypes (GluN2A, B, C, and D), while known fast-off NMDA channel blockers are more selective to GluN2C and D like as Memantine. We will further discuss that the unique future might be beneficial as a fast-onset antidepressant with less side-effects.
Methods: Animals: All experiments were conducted using male rats in accordance with the guidelines by the Institutional Animal Care and Use Committee of Astellas Pharma Inc. Patch clamp recordings: NaCl-based buffer containing 1 mM MgCl2 was used as the extracellular solution. The current was recorded under whole cell patch clamp formation from a HEK cell expressing each subtype of NMDA channel. EEG recordings: Recordings were from freely moving rats with skull screw electrode without any stimulation. Recording continued for 60 min after oral administration of drugs. Locomotor activity in rats: Increase in locomotor activity is thought to be one of the characteristic behavioral side effects associated with NMDA channel antagonists. Timing of recording and the administration route were same to those of the EEG study. Forced swim test in rats; Forced swimming test was performed according to Porsolt's method. A rat was placed in a cylinder containing water with a device to detect the movement of both forepaws of a rat.
Results: One of unique characteristics of ASP0777 was equal selectivity to NMDA channel subtypes even in physiological condition with 1mM Mg++ in bath solution. The IC50 (mM) values for each NMDA channel subtypes are 6.3, 7.6, 6.3, and 6.2 for GluN2A, B, C, and D respectively. As reported previously, the inhibition by Memantine was more selective to GluN2C and GluN2D in the extracellular solution with 1mM Mg++. The values for AZD6765 exhibited the biased selectivity to GluN2C and GluN2D in the physiological condition as well. Except that ASP0777 showed equal selectivity to NMDA channel subtypes, general profile as NMDA channel antagonists was similar to Memantine. Firstly, ASP0777 binds with low affinity to site within the NMDA channel pore. The Ki value (μmol/L) of [3H] MK801 binding to rat brain was 0.43 for ASP0777 and 0.21 for Memantine respectively. Secondly, the unblocking kinetics of ASP0777 was faster than that of Ketamine. Thirdly, both Memantine and ASP0777 showed strong voltage dependency. Administration of NMDA channel blockers (ASP0777, Memantine, and AZD6765) elicited increments of gamma power of spontaneous EEG in rats with a dose dependent manner. When 25% increments of spontaneous gamma power (EC25) were recorded, the maximum drug concentrations in brain were as follows; (mM) [ASP0777] 21 [Memantine] 37, and [AZD6765] 259. The rank order of the EC25 consists with that of IC50 of GluN2A; ASP0777 < Memantine < AZD6765. NMDA channel blockers are known to cause not only the spontaneous gamma power but also hyper locomotion. We confirmed that our testing NMDA channel blockers caused hyperlocomotion with a dose dependent manner as well, and found that rank order of the potency of causing hyper locomotion was totally different from the potency of GluN2A interestingly. The potency of causing hyper locomotion appeared to relate to that of GluN2D antagonism. To verify that ASP0777 has certainly Ketamine-like antidepressants efficacy in preclinical model, we checked the efficacy in rat forced swim model. As previously reported using Ketamine, an administration of ASP0777 in 30 mg/kg p.o. increased an immobility time acutely (1hr later), and then the efficacy was observed even 24hr later of the administration of drug. The administration of ASP0777 in 30 mg/kg p.o. caused significant increment of spontaneous gamma power acutely as well.

Conclusions: Clinical adverse effects including psychotomimetic properties caused by Ketamine are suggested to link to a couple of properties of Ketamine. First property is the slow off-rate of inhibition, which makes large use-dependency. Large use-dependency is thought to cause excessive disinhibition and too much hyper glutamatergic state. Second property is antagonism of NMDA channels conveying GluN2C/D subunits, which are expressed in extra synaptic space. The blocking is shown to relate to behavioral effects caused by phencyclidine including the hyper locomotion. It is generally accepted that GluN2A/B antagonism induces fast-onset antidepressant efficacy. ASP0777, which has both the equal subtype selectivity and the fast-off rate, can offer a unique possibility as antidepressants, which has never been tried in clinical study.
Keywords: ASP0777, Antidepressant, NMDA channel blocker, Ketamine.
Disclosure: Astellas Pharma Inc. (All authors are employee of Astellas).

W214. Individual Differences in the Modulation of Dopamine Signals in the Ventral Striatum by Nicotinic Acetylcholine Receptors

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Background: Variability in the rate in which animals will acquire self-administration of psychostimulants is a preclinical model for vulnerability to abuse drugs in humans. The variability in animals' acquisition rate can be predicted by individual differences in animals' locomotor response to a novel environment. Therefore, we investigated whether the propensity to explore a novel environment might also predict individual differences in the activity of receptors that have been shown to be critical for acquisition behavior. We focused on nicotinic acetylcholine receptors (nAChR) located on dopamine terminals in ventromedial striatum (VMS) given their well-documented ability to modulate rapid dopamine signals that are critical for acquisition behavior. Moreover, activation of nAChRs is critical for amphetamine, cocaine, and nicotine sensitization, and nAChR blockade reduces psychostimulant self-administration.
Methods: Male, Sprague-Dawley rats were used as subjects. In experiment one, we first assessed locomotor activity in an inescapable novel environment for all animals followed by two neurochemical tools to measure modulation of dopamine tone and rapid dopamine signals by nAChR agonists (nicotine) and antagonists (mecamylamine, dihydro-beta-erythroidine). Specifically, we examined the extent to which response to novel environment predicts nAChR-induced modulation of 1.) extracellular dopamine tone in the VMS using microdialysis and 2.) rapid dopamine release and uptake signals using voltammetry in brain slices. In a second experiment, we used voltammetry in anesthetized rats and stimulated pedunculopontine nucleus (PPTg) projections to the ventral tegmental area (VTA) to test whether response to a novel environment predicts the ability of endogenous acetylcholine to modulate the magnitude of rapid dopamine release in the VMS.
Results: Rats with a higher response to a novel environment (HR) demonstrated greater increases in VMS dopamine tone to intra-VTA infusion of nicotine ($r = 0.80$, $p < 0.05$). Intra-VTA infusion of low concentrations of mecamylamine increased VMS dopamine levels in HR rats, but decreased dopamine levels in LR rats. High concentrations of mecamylamine decreased dopamine levels in all rats. There was no difference in dopamine response to electrical stimulation of dopamine in brain slices from HR and LR rats under drug-free conditions. However, the general nAChR antagonist mecamylamine, the Beta2-specific antagonist DHBetaE, and a desensitizing dose of nicotine showed greater inhibition of dopamine release in LR rats under single pulse and low frequency, multiple-pulse stimulations that reflect tonic firing of dopamine neurons. In contrast, there was greater facilitation of dopamine release to nAChR blockade or desensitization in HR rats under multiple-pulse, high-frequency conditions that reflect phasic firing of dopamine neurons. Experiment two revealed that DA release in the VMS following PPTg stimulation is substantially greater in magnitude and longer in time in HR relative to LR rats, and is sensitive to nAChR antagonists. These differences are characterized by a greater number of spontaneous, transient DA release events following PPTg stimulation in HR rats compared to LR rats ($p < 0.05$).
Conclusions: HR rats are more sensitive to elevations in VMS dopamine tone following activation of VTA nAChR with nicotine, and display a previously undocumented elevation of dopamine tone following VTA nAChR blockade. LR rats are more sensitive to the dopamine inhibitory effects of nAChR blockade under tonic firing-like conditions while HR animals are more sensitive to the dopamine facilitative effect of nAChR blockade under phasic firing-like conditions. These data demonstrate an enhanced ability of VTA and VMS nAChRs to facilitate DA release in HR animals following both nicotine and endogenous acetylcholine release from PPTg afferents. HR animals are known to acquire drug self-administration more rapidly, suggesting that these animals may have differential dopamine responses during acquisition and conditioned learning that is contingent upon differential modulation of dopamine signals by nAChRs. Indeed, the increased sensitivity to nAChR-induced facilitation of dopamine signals elicited by phasic-like stimulation parameters may be mechanistically linked to faster and more robust acquisition of drug self-administration.
Keywords: dopamine, acetylcholine, nicotinic receptor, nicotine.
Disclosure: Nothing to Disclose.

W215. Antagonism of p38α MAPK Signaling Corrects Receptor Hypersensitivity and Altered Social Behavior in the SERT Ala56 Genetic Mouse Model of Autism Spectrum Disorder

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Background: Autism Spectrum Disorder (ASD) is a common neurodevelopmental disorder exhibiting language

and communication deficits, perturbations in social interactions, and repetitive behaviors. Owing in part to a still limited understanding of the mechanistic basis for ASD, treatments are lacking for the core symptoms of the disorder. Although elevated blood serotonin (5-HT) levels are found in a significant number (25-30%) of ASD patients, how this biomarker relates to ASD etiology is unknown. In prior ASD genetic studies, we discovered 5 rare, genetic variants in the SLC6A4 gene encoding the 5-HT transporter (SERT) that lead to elevated SERT function (Sutcliffe et al. 2005). In vivo expression of SERT Ala56 in a knock-in mouse model results in multiple ASD-like phenotypes, including hyperserotonemia, repetitive behaviors and deficits in social interactions and communication (Veenstra-VanderWeele et al, 2012). Notably, SERT Ala56 mice display a p38 MAPK-dependent hyperphosphorylation of SERT within the CNS, consistent with our prior findings that activation of p38α MAPK elevates SERT function in vitro and in vivo (Zhu et al. 2006, Zhu et al. 2010). These findings suggest that the hyperfunction of SERT Ala56 and resulting physiological and behavioral phenotypes are due to unopposed p38α MAPK phosphorylation of the transporter. We hypothesized, therefore, that pharmacologic inhibition of p38α MAPK might attenuate or reverse one or more phenotypes in the SERT Ala56 model. Recently, Watterson et al. (2013) reported the development of a highly selective, brain-penetrant, p38 MAPK inhibitor, MW108 (N,N-dimethyl-6-(naphthalene-2-yl)-5-(pyridine-4-yl)pyridazin-3-amine), with evidence accruing to support utility in brain injury models (Watterson et al. 2014). Here we report our efforts to reverse ASD features of adult SERT Ala56 mice with MW108.

Methods: To assess whether MW108 can attenuate p38 MAPK-mediated stimulation of SERT activity, we monitored [3H]5-HT uptake in neuroectodermal SK-N-MC cells that stably express WT human SERT with or without treatment with the p38 MAPK activator anisomycin (0.1 nM for 15 min). To explore the utility of MW108 in vivo, we treated adult (8-12 wks) male SERT Ala56 mice or WT littermates with MW108 (10 mg/kg, i.p., QD, 1 week) or vehicle, followed by tests of 5-HT receptor sensitivity and social interactions. We assessed 5-HT2A receptor sensitivity using 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI, 1.0 mg/kg, i.p.)-induced head twitch assays and quantified 5-HT1A receptor sensitivity using 8-hydroxy-2-(di-n-propylamino)-tetraline (8-OH-DPAT, 0.1 mg/kg, s.c.)-induced hypothermia assays. To monitor social behavior, we examined pair-wise interactions between animals in the Tube Test.

Results: Acute treatment (5 min pretreatment, 1 and 10 nM) with MW108 blocked the ability of anisomycin to enhance SERT activity in transfected SK-N-MC cells, consistent with a role for p38α MAPK in SERT stimulation. DOI and 8-OH-DPAT treatment of SERT Ala56 animals demonstrated elevated 5-HT2A and 5-HT1A receptor sensitivities in head-twitch and hypothermia assays, respectively, as previously described (Veenstra-VanderWeele, 2012). Chronic MW108 treatments eliminated the 5-HT2A receptor hypersensitivity of SERT Ala56 animals and attenuated, albeit non-significantly, 5-HT1A receptor hypersensitivity. Finally, MW108 treatment rescued the social phenotype of SERT Ala56 mice as examined in the Tube Test.

Conclusions: These are the first studies, to our knowledge, that document pharmacologic reversal of ASD-like phenotypes through the inhibition of p38 MAPKα signaling. Our ability to reverse receptor and behavioral phenotypes through treatments given to adult animals argues that some deficits induced by the SERT Ala56 model are dependent upon p38α MAPK signaling and are supported by ongoing functional perturbations rather than irreversible consequences of altered 5-HT action during development. We speculate that, whereas SERT Ala56 is a rare variant, the insights gained from our studies may apply to other means of elevating SERT function, as with immune signaling-induced p38α MAPK activation (Zhu et al, 2010). Altogether, our studies support a further evaluation of p38 MAPKα-based treatments as potential therapies for ASD.

Keywords: Autism Spectrum Disorder, Serotonin Transporter, p38 MAPK, Serotonin.

Disclosure: Nothing to Disclose.

W216. Pituitary Adenylate Cyclase-activating Polypeptide (PACAP) Disrupts Motivation, Attention, and Social Interaction

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Background: Exposure to severe or prolonged stress can cause psychiatric illnesses including anxiety and depressive disorders. The mechanisms by which stress induces these illnesses are not fully understood. Recent work has shown that PACAP (pituitary adenylate cyclase-activating polypeptide) is released in the brain in response to stress and produces anxiety-related behaviors. For example, PACAP treatment in rats causes persistent anxiogenic responses as reflected by increases in acoustic startle. It is well established that stress can also induce anhedonia (reduced ability to experience reward), and disrupt cognition, motivation, and social interaction. The present studies were designed to investigate how PACAP affects behaviors that reflect these core features of mood disorders.

Methods: The intracranial self-stimulation (ICSS) test was used to assess whether PACAP induces anhedonia. Adult male Sprague-Dawley rats were implanted with an intracerebroventricular (ICV) cannula and a lateral hypothalamic (LH) electrode and trained in the rate-frequency variant of the ICSS procedure. When reward thresholds were stable (<10% variability) for 3 consecutive days, rats were infused with vehicle (artificial cerebral spinal fluid [aCSF]) or PACAP (0.25-1.0 μg) and tested immediately for 90 min. Rats were tested each day for 8 days without any additional treatment. The 5-choice serial reaction time task (5CSRTT) was used to examine if PACAP disrupts attention, impulsivity, and motivation. A separate cohort of rats were food-restricted to 85% of free-feeding weight and trained in the 5CSRTT until reaching criteria (>60% correct responses and <20% omissions on 3 consecutive days). Following ICV cannula implantation and re-stabilization of performance, rats were infused with vehicle or PACAP

(0.25-1.0 μg) and tested in 5CSRTT 1 hr later and each day for 8 days post-treatment. Finally, we examined if PACAP alters social interaction and social withdrawal. One week after ICV cannula implantation, a third cohort of rats was infused with vehicle or PACAP (0.25-1.0 μg) and placed in a 60 x 60 x 40 cm Plexiglas chamber with a weight-matched partner rat 1 hr later and with a new partner rat 8 days later. Social behavior was videotaped for 10 min and scored by an observer blinded to treatment condition.
Results: In the ICSS test, PACAP treatment (at the 0.5 and 1.0, but not 0.25 μg dose) produced acute increases in ICSS thresholds (indicative of anhedonia), but did not alter max rates, a putative index of motor capabilities. In the 5CSRTT, rats treated with PACAP (at the 0.5 and 1.0, but not 0.25 μg dose) exhibited acute decreases in % correct and number of head entries, and increases in % omissions. Only rats treated with 1.0 μg PACAP exhibited decreases in accuracy. In the social interaction test, PACAP (at the 0.5 and 1.0, but not 0.25 μg dose) significantly decreased social behaviors (e.g. grooming, sniffing, following partner rat). The highest dose of PACAP (1.0 μg) also produced anxiety-like behaviors (decreased time spent in the center of the arena) during the social interaction test. Interestingly, unlike previously reported effects on acoustic startle, the effects of PACAP on these behaviors were not persistent.
Conclusions: We show that PACAP produces dose-dependent disruptions in motivation, attention, and social interaction. Our findings complement previous work showing that central administration of PACAP induces anhedonia and increases anxiety-related behaviors. A more comprehensive understanding of the impact and persistence of PACAP on symptoms associated with mood disorders will elucidate how stress contributes to psychiatric illness, and facilitate the development of new medications for stress-related disorders.
Keywords: PACAP, Anhedonia, Attention, Social Interaction.
Disclosure: Dr. Carlezon has a US patent covering the use of kappa-opioid receptor antagonists in the treatment of depressive disorders (Assignee: McLean Hospital). In the last 3 years, Dr. Carlezon has received compensation for professional services from The American College of Neuropsychopharmacology.

W217. Dopamine D2/3 Receptor Antagonism Reduces Activity-based Anorexia: Implications for Anorexia Nervosa Treatment

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Background: Anorexia Nervosa (AN) is an eating disorder characterized by severe hypophagia, emaciation, hyperactivity, intense fear of gaining weight, and body image distortion. Activity-based anorexia (ABA) refers to the dramatic weight loss, hypophagia, and paradoxical hyperactivity that develops in rodents exposed to running wheels and scheduled feeding, and provides a model for aspects of AN. The atypical antipsychotic olanzapine was recently shown to reduce ABA in rodents and symptoms of AN.
Methods: We examined which component of the complex pharmacological profile of olanzapine reduces ABA behavior. In separate studies, mice received chronic treatment with multiple doses of 5-HT2A/2C, 5-HT3, dopamine D1, D2, D3, or D2/3 antagonists, and were assessed for food intake, bodyweight, wheel running, and survival in the ABA paradigm. Furthermore, we directly compared the effects of olanzapine and the D2/3 antagonist amisulpride on ABA.
Results: Chronic treatment with the D2/3 receptor antagonists eticlopride or amisulpride robustly increased bodyweight, food intake, and survival, defined as the number of days remaining above 75% of initial bodyweight. Furthermore, amisulpride produced larger increases in food intake than olanzapine. Finally, treatment with either the D3 receptor antagonist SB 277011A or the D2 receptor antagonist L-741,626 also increased survival. The remaining drug treatments either had no effect, or worsened ABA. All observed effects were absent during ad libitum feeding conditions.
Conclusions: In sum, selective antagonism of D2 and/or D3 receptors robustly reduces ABA behavior. Further studies investigating the mechanisms by which D2 and/or D3 receptors regulate ABA, and the efficacy for D2/3 antagonists to treat AN, are warranted.
Keywords: anorexia nervosa, food intake, body weight, wheel running.
Disclosure: Nothing to Disclose.

W218. "Derisking" Addiction-Associated Cell Adhesion Molecules as Targets for Antiaddiction Medications Development

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Background: Genes that encode cadherin 13 (CDH13) and receptor type protein tyrosine phosphatase D (PTPRD), repeatedly associated with addiction-related phenotypes by GWAS signals of modest magnitude, provide potential targets for development of antiaddiction medications.
Methods: Association between genomic markers and levels of mRNA expression in postmortem cerebral cortex. Behavioral testing in wildtype (+/+), heterozygous and homozygous CDH13 and PTPRD KO mice (+/- and -/-) using conditioned placed preference and oral consumption and other comparison testing. Comparison physiological and behavioral testing.
Results: PTPRD and CDH13 genomic markers displayed association with 60 – 70% individual differences in levels of expression of these genes in postmortem brains. Mice with reduced CDH13 or PTPRD expression displayed reduced preferences for places paired with 10 mg/kg cocaine doses. There was significant evidence for left-shifts of the dose response relationships in both CDH13 and PTPRD knockouts. Mice with reduced CDH13 expression displayed selective alterations in cerebral cortical levels of dopamine and its metabolites. In initial studies, these animals displayed reductions in densities of dopamine (dopamine transporter-immunoreactive) fibers in infralimbic and nearby cortical regions. By contrast, the CDH13 knockout

mice displayed normal strength, no deficits in learning, and near normal performance in other testing. PTPRD heterozygotes also displayed normal mnemonic functions in Morris water maze testing, though homozygous knockouts were substantially impaired.
Conclusions: These data indicate reasonable potential risk/benefit profiles for compounds that might act at CDH13 or PTPRD to alter addiction. Data from the CDH13 knockouts provides apparent selectivity for dopamine systems that are specifically implicated in aspects of addiction.
Keywords: cell adhesion molecules, addiction, alcohol abuse, translational.
Disclosure: Nothing to Disclose.

W219. Oral Consumption of Ethanol, Nicotine and Methamphetamine in Cadherin 13 Knockout Mice

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Background: Cadherin 13 (CDH13) is a cell adhesion molecule that shows moderate, replicated genetic associations with addiction and nicotine cessation. We have found that this allelic variation is associated with reduced expression ($\sim$50%) of CDH13 mRNA. We have previously shown that CDH13 knockout (CDH13 KO) mice have a leftward shift in the dose response for cocaine CPP. The current study extends these findings by examining oral consumption of ethanol, nicotine and methamphetamine in CDH13 KO mice.
Methods: Ethanol, nicotine and methamphetamine consumption was compared in male and female wildtype (+/+) and CDH13 KO mice (+/- and -/-) using previously validated procedures. Voluntary ethanol (2–32% v/v), nicotine (5-320 μg/mL), and methamphetamine (5-160 μg/mL) consumption were compared in two-bottle, 24 hr access, home-cage preference tests (versus water). The concentration increased every 2 days) and water. In separate groups of mice the escalation of ethanol intake (8% ethanol versus water, 2 days per week, M/Th, with only water available on intervening days) was measured over 6 weeks.
Results: In the initial ethanol consumption study, consumption of the highest concentration of ethanol was increased in female CDH13 -/- mice. When consumption was limited to 2 days per week in the escalation study, greater escalation of ethanol intake was observed in female CDH13+/- mice. Little escalation, and lower levels of ethanol consumption overall, were observed in male mice. Increased consumption of the highest nicotine concentration was observed in female CDH13+/- and -/- mice. By contrast, reduced consumption of the highest 2 nicotine concentrations was observed in male CDH13+/- mice compared to both CDH13+/+ and CDH13 -/- mice. No differences in oral methamphetamine consumption were observed between genotypes, although, again, females consumed more than males.
Conclusions: These data indicate that reductions in the expression of CDH13, as predicted by human genetic and post mortem gene expression studies, affect oral consumption of ethanol and nicotine. Furthermore, under some conditions, including those producing escalation of ethanol intake, heterozygous deletion of CDH13 affects ethanol and nicotine consumption. This degree of reduction of CDH13 expression is in the range of the differences in human expression of CDH13 that we have previously observed. In the cases of both ethanol and nicotine consumption the effects were highly sex-dependent. It is not known whether the genetic associations between CDH13 markers and addiction in humans are also sex-dependent, but this will obviously be an important consideration in future human genetic and mouse studies.
Keywords: Addiction, Ethanol, Nicotine, Cell adhesion molecule.
Disclosure: Nothing to Disclose.

W220. Effects of Self-administered Methamphetamine on Learning-to-Learn and Cognitive Flexibility in Nonhuman Primates

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Background: The worldwide use of amphetamines exceeds that of heroin and cocaine combined, and the illicit use of methamphetamine, in particular, presents a global health challenge. Although use of methamphetamine (MA) has plateaued somewhat in the US and Europe, prevalence is increasing in Central and South America as well as the Middle East. Long-term chronic exposure to MA has been related to profound neural impact including, but not limited to, damage to monoamine nerve terminals. In turn, neural changes following repeated MA administration may be related to adverse effects on learning and other cognitive performance. However, the characterization of such neurobehavioral deficits remains incomplete. The present study assessed the effects of ongoing intravenous MA self-administration on touchscreen-based animal models of learning and cognitive flexibility in nonhuman primates.
Methods: Daily 2-hr self-administration sessions using the optimal self-administered dose of MA (determined in dose-effect studies) were conducted throughout the present studies. After 30 self-administration sessions, a second daily session in which subjects responded on a touchscreen was introduced. Prior to MA self-administration (i.e., 20-hr after the previous day's session), monkeys engaged in a repeated acquisition task (i.e., an animal model of learning) in which changes in the rate of discrimination learning were assessed over the successive presentations of novel stimulus pairs. Subsequently, the discrimination reversal task (i.e., an animal model of cognitive flexibility) was introduced in which the subject was required to inhibit a previously reinforced response and respond to the initially ineffective stimulus to obtain reward. Time course assessments were also conducted in which the time between self-administration and touchscreen tasks was reduced. Finally, a withdrawal condition was studied in which cognitive performance was assessed following discontinuation of MA self-administration.

Results: Results indicated that ongoing MA self-administration produced markedly deleterious effects on the development of learning sets in discrimination learning. Importantly, the magnitude of adverse effects on learning was highly correlated with the level of daily MA intake among individual subjects. Following extended exposure to the task, subjects were eventually able to learn novel discriminations as rapidly as drug-free control subjects. Discrimination reversal was largely unaffected by daily MA self-administration. However, when the interval between the MA self-administration session and touchscreen session was reduced, reversal performance was more vulnerable to the direct adverse effects of MA. No disruption in either learning or reversal performance was observed following discontinuation of MA self-administration.
Conclusions: Taken together, these results indicate that daily MA self-administration has dramatic, deleterious effects on learning-to-learn simple discrimination. Despite the fact that discrimination reversal performance has previously been shown to be particularly sensitive to psychoactive drugs under acute administration, no significant effects were observed in the present chronic studies. However, when assessing the direct effects of MA on these cognitive performances by decreasing the time between MA intake and the touchscreen session, reversal learning was more sensitive than discrimination learning. This highlights interesting differences between the direct acute effects of MA and the consequences of chronic exposure. The lack of withdrawal-related disruption on these measures was not surprising in view of the absence of a clear withdrawal syndrome that occurs after abstinence from MA. These data reveal important features regarding the impact of chronic MA use on different dimensions of cognitive function.
Keywords: methamphetamine, touchscreen, cognition, monkey.
Disclosure: Nothing to Disclose.

W221. A Novel Depression Treatment Targeting the Active Ionic Mechanisms of Natural Resilience

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Background: There is an urgent need for mechanistically targeted antidepressant therapies, as less than half of major depressive disorder patients achieve full remission with symptom-treating, monoamine-based antidepressants. There is new hope coming from the exciting advances in the understanding of the molecular, cellular and circuitry mechanisms underlying resilience to social stress-induced depression. Highly consistent evidence shows that natural resilience is an active stress-coping process. Specifically, it has been shown that social defeat stress induces a hyperactivity of ventral tegmental area (VTA) dopamine neurons, which directly encodes a depressive (susceptible) phenotype. Further, it was recently demonstrated that development of resilience to chronic social defeat stress occurs through an active upregulation of voltage-gated potassium (K+) channels, which counteracts the pathogenic hyperactivity of VTA dopamine neurons. Yet, naturally acting antidepressants that target this active ion channel mechanism of resilience have not been explored. Here we demonstrate that among these actively upregulated K+ channels, KCNQ plays a critical role in the development of resistance to chronic social stress. Importantly, we show that KCNQ channel openers consistently show antidepressant efficacy, which mimics the active resilience ionic mechanism.
Methods: Following a well-established chronic social defeat stress paradigm, we separated susceptible and resilient behavioral phenotypes using a social interaction test. Utilizing tyrosine hydroxylase (TH)-GFP mice (C57BL/6) to identify VTA dopamine neurons in an in vitro slice preparation, we demonstrated that resilient animals maintain healthy dopamine neuron activity through an upregulation of K+ channels. We then evaluated responsivity of a variety of pharmacological agents. Utilizing combination of viral and transgenic mouse approach, we specifically expressed KCNQ3 in VTA dopamine neurons by injecting a Cre-inducible HSV-LS1L-KCNQ3-eYFP into the VTA of TH-Cre mice. In in vivo pharmacological experiments, susceptible or resilient mice were subjected to local drug infusions to the VTA immediately prior to behavioral testing or 24 hours post-repeated intraperitoneal injection.
Results: We first replicated the previously reported finding that K+ channels are upregulated in VTA dopamine neurons following chronic social defeat stress selectively in mice that are found to be resilient. Next, to identify specific K+ channel subunits involved in this behavior we directly infused a selective inhibitor of KCNQ channels, XE-991, into the VTA of resilient mice. Inhibition of KCNQ channels in resilient mice resulted in the depressive behavior phenotype showing clear social avoidance. This demonstrates that KCNQ channels are necessary and crucial for the development of a resilient phenotype. Next, to determine if upregulation of this KCNQ current alone is sufficient to convert previously social avoidant and anhedonic mice to resilience, we selectively increased KCNQ3 channel in the VTA dopamine neurons of susceptible mice, reducing the stress-induced hyperactivity of these neurons. We observed a reversal of the susceptible phenotype, with increased social interaction, an increase in sucrose preference and a reduction of the time spent immobile during a forced swim test. Together these data provide direct evidence that KCNQ channels are valid therapeutic targets for stress-induced depressive behavior. Therefore, we utilized currently available pharmacological agents and tested whether direct infusion of KCNQ channel openers to the VTA would have antidepressant actions. Directly following a single infusion of flupirtine, BMS-204352 and retigabine, the behavioral phenotype of the susceptible mice is reversed. Towards our translational goal we further tested whether retigabine, a FDA-approved drug to treat partial epilepsies, would have treatment efficacy with repeated intraperitoneal injections and found a similar, highly consistent antidepressant efficacy.
Conclusions: There is an increasing amount of research demonstrating that resilience is an active stress-coping process, with the upregulation of both genes and ionic

functions. With the goal of therapeutically mimicking the naturally resilient active ionic mechanism, we demonstrated the efficacy of a series of pharmacological potentiators of KCNQ channels for antidepressant action. These findings demonstrate that K + channel openers counteract the pathophysiological hyperactivity of VTA dopamine neurons and pharmacological potentiation of this naturally occurring resilience functions as an "active" antidepressant, which is conceptually different from classic depression treatment.

Keywords: resilience, KCNQ, antidepressant, social defeat stress.

Disclosure: Nothing to Disclose.

W222. Efficacy of Functionally-Selective Dopamine 2 Receptor Ligands on Schizophrenia-like Behaviors

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Background: Recent experiments have shown that ligand binding can induce conformational changes in G protein-coupled receptors (GPCRs) that lead to differential signaling events. These signaling cascades are controlled by the cellular milieu in which they occur and are organized into networks that are highly regulated to generate their unique responses. Ligand binding to GPCRs can activate, inhibit, or exert no effects on the G protein-dependent signaling pathway while serving the same or diverse actions on a G protein-independent pathway through β-arrestin (βArr). This property of functional selectivity has been established for a few GPCRs; however, none of the current ligands or drugs were developed with this property in mind. All current FDA-approved antipsychotic drugs bind to the dopamine D2 receptor (D2R). In vitro cellular-based experiments have shown that haloperidol, clozapine, ziprasidone, chlorpromazine, risperidone, quetiapine, olanzapine, and aripiprazole also influence βArr2 recruitment to the D2R, while serving as inverse to partial agonists or antagonists for Gi/o protein activation. Due to these actions, our purpose was to develop functionally-selective D2R compounds that may have efficacy in treating individuals with schizophrenia and other related disorders.

Methods: The Gi/o-biased (UNC2438) and the βArr-biased (UNC9975) compounds were evaluated for their effects on suppression of hyperlocomotion in the open field and on restoration of prepulse inhibition (PPI), two separate tests for schizophrenia-like behavior in rodents. The compounds were tested in the amphetamine (AMPH) and phencyclidine (PCP) pharmacological models with C57BL/6 mice and/or in the dopamine transporter knockout (DAT-KO) and NR1 knockdown (NR1-KD) genetic models of schizophrenia-like behavior. Wild-type (WT) and βArr2-KO mice served as controls for the specificity of the βArr-biased compound.

Results: In the open field, the βArr-biased compound UNC9975 reduced the hyperactivities of DAT-KO and NR1-KD mice. Similarly, the Gi/o-biased compound UNC2438 also decreased both AMPH- and PCP-stimulated hyperlocomotion in C57BL/6 mice. Parenthetically, the specificity of UNC9975 in βArr2 mice in the open field has been published Allen et al, 2011 PNAS). In PPI UNC9975 rescued this behavior in DAT-KO and NR1-KD mice. In the βArr2 mice, 0.2mg/kg UNC9975 was sufficient to restore PCP-disrupted PPI in WT animals whereas 1 mg/kg was required to normalize PPI in the βArr2-KO mice. By comparison, UNC2438 failed to exert any effects on PCP-disrupted PPI in C57BL/6 mice.

Conclusions: The βArr-biased compound UNC9975 was efficacious in reducing hyperactivity in the open field in the DAT-KO and NR1-KD mice, animals that are persistently hyperdopaminergic and hypoglutamatergic, respectively. Similarly, the Gi/o-biased compound UNC2438 also decreased hyperactivity in the open field in the AMPH and PCP models of schizophrenia-like behavior; however, this compound was more efficacious in the AMPH model. UNC9975 also rescued PPI in the DAT-KO and NR1-KD mice. Specificity of this response was demonstrated in the βArr2 mice, where the dose of UNC9975 had to be increased 5-fold to normalize PCP-disrupted PPI in the βArr2-KO animals compared to the WT controls. This effect may be due to some off-target actions of the compound. By comparison, the UNC2438 was without effect on PCP-disrupted PPI in C57BL/6 mice. Collectively, these findings indicate that Gi/o- and βArr-biased ligands can exert differential effects on behavior and these responses may have relevance to schizophrenia and other related disorders in humans.

Keywords: Schizophrenia-like Behavior, Mouse Models, Dopamine 2 Receptor, Functional Selectivity.

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W223. Adolescent Mice Exposed to THC Manifest Persistent Neuroadaptive Changes in Adult Cerebellum

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Background: Compared with adult onset of marijuana use, early adolescent users of marijuana are more susceptible to its associated adverse consequences: addiction, cognitive impairment, altered brain morphology, IQ decline, and psychosis. Brain imaging has begun to reveal neuroanatomical regions that may contribute to these diverse consequences. Functional neuroimaging in adults has identified fronto-cerebellar dysfunction and morphological changes associated with chronic marijuana use. Adolescent marijuana users reportedly display significantly larger posterior cerebellar vermis volumes than non-using controls. These differences conceivably are pathological as they are associated with reduced executive functioning. The cerebellum expresses a high density of cannabinoid type 1

receptors that are implicated in neuronal diversification of the developing brain and other functions. We postulated that THC, the main psychoactive constituent of marijuana, affects adolescent cerebellum development or function by modifying expression of genes implicated in dopamine and glutamate signaling, in guidance of neural circuitry during neurodevelopment, and in other functions that may be relevant to the long term consequences of early and frequent marijuana use.
Methods: We treated adolescent rats (PND 28) with THC (10 rats; 1.5 mg/kg i.p., every 3rd day) or vehicle (10 rats). Five drug-treated and five vehicle control rats were euthanized 24 hr after the last injection (PND 50) and the remaining 10 rats were euthanized 2 weeks later in early adulthood (PND 64). Genes (46) were selected on the basis of their function in synaptic signaling (receptors, transporters), neurodevelopment, including guidance of dopamine circuitry during adolescent brain development, neuroadaptation and stress response. The role of the majority of these genes in cerebellum development and activity is unknown. Gene expression levels were measured following mRNA isolation from cerebellum and cDNA synthesis. Expression of the selected genes were measured using real-time PCR on a LightCycler 480 using rat-specific, intron-spanning when possible, primers and probe-based qPCR assays with the Universal Probe Library system. At least three technical replicates were performed for each gene in every tissue sample. Data were analyzed using the $\Delta\Delta$Ct method, normalizing the raw data to beta actin (ACTB) as a housekeeping gene. The average fold change values with standard error were analyzed for statistical significance, using a two-tailed, paired t-test.
Results: Administered intermittently for three weeks, THC altered expression of genes in cerebellum in animals euthanized 24 h after the last dose during the adolescent period. Altered gene expression differed in magnitude and direction of change in animals euthanized two weeks later during early the transition to adulthood, or compared with vehicle controls. The most significant changes, largely down-regulated genes, emerged two weeks following the last drug dose. DCC, neuropilin1 and Dusp6 were down-regulated two weeks after THC cessation. DCC and possibly neuropilin regulate developmental organization of meso-corticolimbic dopamine circuitry during adolescence and DCC is implicated in a genotype association with schizophrenia. Dusp6 (or MKP3) is implicated in regulating dopamine transporter trafficking. Other genes associated with the development of neural circuitry were down-regulated two weeks after THC administration (NCAM, Unc5b, Mmp1). Genes that respond to stress, injury and neuronal death (CRMP1, Sqstm1) were also donw-regulated. Genes encoding glutamate receptors, a glutamate transporter, and transcription factors, some of which are implicated in schizophrenia, were also down-regulated after two weeks (CB1, GluR2, NR2A, EAAC1, CRMP1, CRMP2, YBX1). In contrast, tyrosine hydroxylase was upregulated.
Conclusions: Neurons and neuronal circuits respond to repeated drug exposure by adapting to abnormal signals. The long term effects of early, heavy marijuana use on cognition, IQ, addiction, and psychosis, indicate that marijuana promotes profound neuroadaptive changes in the developing adolescent brain. We focused on expression of selected genes in cerebellum, a brain region implicated in the long term effects of marijuana. Repeated administration of THC to adolescent rats dramatically reduced a number of genes in cerebellum, two weeks after the last THC dose and during the transition from adolescence to adulthood. Reduced expression of the gene encoding the CB1 receptor, the immediate target of THC, conceivably triggers a cascade of down-regulation of other expressed genes implicated in guiding dopamine circuits, synaptic transmission, plasticity, glutamate receptors, neurogenesis, schizophrenia, and stress response. Robust changes were detected two weeks after drug cessation, indicating enduring effects of THC. Our findings provide important leads for investigating the molecular mechanisms underlying THC-induced cerebellar deficits.
Keywords: marijuana, THC, adolescent development, schizophrenia.
Disclosure: Prexa Pharmaceuticals (consultant) US Department of Justice (consultant) Rivermend Health, Inc (scientific advisory board, consultant) National Football League (consultant).

W224. Levodopa Reverses Cytokine-induced Reductions in Striatal Dopamine Release

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Background: Recent data indicate that dopamine neurons play an important role in multiple depressive symptoms, and neuroimaging findings suggest that inflammatory cytokines target the ventral striatum and dopamine to mediate depressive symptoms of anhedonia and psychomotor slowing. We have previously reported that chronic administration of a peripheral inflammatory cytokine, interferon (IFN)-alpha, decreases dopamine release in the basal ganglia (striatum) in a rhesus monkey model of cytokine-induced depressive and anhedonic behavior. However, the mechanisms by which cytokines decrease dopamine release are currently unknown. Herein we present the first mechanistic data regarding how cytokines decrease dopamine to contribute to depressive symptoms.
Methods: Rhesus monkeys were administered interferon IFN-alpha (20 MIU/m2 s.c.) for 4 weeks and in vivo microdialysis with amphetamine stimulation was conducted either in the presence or absence of the dopamine precursor levodopa (L-DOPA) administered via reverse in vivo microdialysis and compared to control conditions.
Results: Cytokine-induced reductions in striatal dopamine release during chronic IFN-alpha administration were completely restored by L-DOPA, in the absence of an increase in the 3,4-dihydroxyphenylacetic acid (DOPAC) to dopamine ratio (DOPAC/dopamine). These findings indicate that inflammatory cytokines may deplete dopamine synthesis without affecting vesicular packaging or release mechanisms.
Conclusions: Cytokine-induced reductions in dopamine synthesis may explain our recent neuroimaging findings in depressed patients that exhibit increased inflammation, including decreased corticostriatal functional connectivity. Furthermore, the reversal of cytokine effects on dopamine

with L-DOPA provides a framework for future studies investigating the use of therapeutic strategies that increase dopamine synthesis to improve depressive symptoms in patients with increased inflammation.
Keywords: cytokines, dopamine, anhedonia, animal models.
Disclosure: Nothing to Disclose.

W225. Subjective and Reinforcing Effects of Tobacco Smoke Constituents in Nonhuman Primates

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Background: Nicotine in tobacco smoke is the principal psychoactive chemical responsible for maintaining tobacco consumption. Recently, however, a growing appreciation of the complexity of tobacco smoke, which contains more than 7000 different chemical constituents in addition to nicotine, has led to the suggestion that some of these compounds may also contribute to tobacco addiction. The levels of some constituents of tobacco smoke, e.g, nornicotine, are well documented in cigarettes; however, their role in tobacco addiction, including their interactions with nicotine, have not been well studied. Previous evidence suggests that some such tobacco smoke constituents may augment nicotine's psychoactive properties and/or produce such effects in their own right, whereas other constituents (e.g., cotinine) appear to be behaviorally inactive. Findings such as these indicate the strong need for a better understanding of the possible role of minor tobacco alkaloids in tobacco consumption and conceivably, in future manipulations of tobacco composition. The present studies were conducted to address this need by assessing, respectively, the nicotine-like discriminative-stimulus and reinforcing effects of minor tobacco alkaloids (e.g., nornicotine, anabasine, anatabine, myosmine, and cotinine) in NHP. The effectiveness with which non-nicotine tobacco constituents engender nicotine-like discriminative-stimulus and reinforcing effects in monkeys may serve as a preclinical indicator of their pharmacological actions in smoking behavior.
Methods: In drug discrimination studies, the ability of minor tobacco alkaloids to engender nicotine-like discriminative-stimulus effects and, separately, to modify nicotine's stimulus properties was determined in squirrel monkeys (n = 4) trained to discriminate a highly potent nicotine-like agonist [(+)-epibatidine] from vehicle. In IV self-administration studies, second-order fixed-interval (SO-FI) schedule procedures in NHP (n = 3) were utilized to determine whether selected minor tobacco alkaloids (e.g., anatabine) exhibit nicotine-like reinforcing effects.
Results: Results from drug discrimination studies show that nicotine and minor tobacco alkaloids engendered full (nornicotine, anabasine, myosmine, anatabine), or no (cotinine) substitution for (+)-epibatidine. Further, time course data also show that the stimulus effects of minor tobacco alkaloids (anatabine and myosmine) lasted longer than those of nicotine. In interaction studies, combining ED50 doses of nicotine and minor tobacco alkaloids (nornicotine, anabasine, myosmine, or anatabine) that produced (+)-epibatidine-like discriminative-stimulus effects resulted in the full expression of (+)-epibatidine-like stimulus properties. Results from our self-administration studies show that nicotine (0.0032–0.032 mg/kg/injection) reliably produced dose-related IV self-administration behavior under the SO-FI schedule, with peak rates of responding during availability of the unit dose of 0.01 mg/kg/injection. In contrast, the minor tobacco alkaloid anatabine (0.01–0.1 mg/kg/injection) failed to maintain IV self-administration under the SO-FI schedule; response rates were no greater than for vehicle. Importantly, the highest unit dose of anatabine (0.1 mg/kg/inj) produced observable adverse reactions (e.g., emesis), precluding the study of higher doses.
Conclusions: Our findings from drug discrimination studies suggest that non-nicotine tobacco constituents may differentially contribute towards maintaining long-term tobacco consumption. Furthermore, the full generalization engendered by combined effective doses of minor tobacco alkaloids and nicotine suggests that these constituents may augment the abuse-related stimulus effects of nicotine. Interestingly, data from ongoing IV drug self-administration studies in monkeys show that the minor tobacco alkaloid anatabine does not maintain nicotine-like self-administration behavior under SO-FI schedule conditions–even at doses that produce observable adverse effects. These results suggest that anatabine likely does not play a major role in tobacco addiction.
Keywords: Nicotine Addiction, Minor Tobacco Alkaloids, Nonhuman Primates, Behavioral Pharmacology.
Disclosure: Nothing to Disclose.

W226. 4-Cl-Kynurenine, a Pro-Drug of a Selective Glycineb NMDA Receptor Antagonist, Induces Rapid and Sustained Antidepressant Effects without Ketamine-related Side Effects

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Background: Major depressive disorder (MDD) afflicts approximately 17 percent of the world population. Although antidepressant medications are available, many patients remain treatment-resistant, and currently used drugs take several weeks to be effective. Evidence suggests actions of the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist ketamine as a rapid-acting treatment for MDD. However, ketamine's clinical potential is limited by its addictive and psychotomimetic properties. We hypothesized that blockade of the glycineB co-agonist site of the NMDA receptor with the selective antagonist 7-Cl-kynurenic acid (7-Cl-KYNA), delivered via systemic administration of its brain-penetrant bioprecusor 4-Cl-kynurenine (4-Cl-KYN), would result in rapid and sustained antidepressant actions, with minimal adverse effects.
Methods: Male CD-1 mice (8-10 weeks old) received drugs intraperitoneally (i.p.). We measured extracellular hippocampal 7-Cl-KYNA levels via microdialysis following a

single injection of 4-Cl-KYN (25 mg/kg) or 7-Cl-KYNA (25 mg/kg). Antidepressant efficacy of 4-Cl-KYN was assessed in the forced-swim (FST) and tail-suspension (TST) tests 1 hour following treatment (1, 5, 25, 125 mg/kg). The sustained antidepressant potential of 4-Cl-KYN (25 mg/kg) was compared to ketamine (10 mg/kg), 7-Cl-KYNA (1 and 25 mg/kg), and fluoxetine (20 mg/kg) in the FST and/or learned helplessness paradigm (LH) 24 hours and/or 7 days after treatment. We also investigated and compared the rewarding effects of 4-Cl-KYN (25 and 125 mg/kg) and ketamine (10 mg/kg) using the conditioned-place paradigm. The psychotomimetic potential of 4-Cl-KYN (25, 125 and 375 mg/kg) was assessed in the pre-pulse inhibition test. Acquisition and development of locomotor sensitization and stereotypic behaviors were characterized following administration of 4-Cl-KYN (25 and 125 mg/kg).
Results: 4-Cl-KYN induced a time-dependent conversion to 7-Cl-KYNA in hippocampus, reaching peak levels ~1.5 hour following injection. Minimal levels of 7-Cl-KYNA that were not sustained were observed following peripheral administration of 7-Cl-KYNA. Administration of 4-Cl-KYN resulted in rapid, dose-dependent antidepressant effects in both FST and TST one hour following treatment. Following a single administration, this effect persisted for 24 hours in the FST, and 24 hours and 7 days in the LH. A single administration of 7-Cl-KYNA or fluoxetine did not result in antidepressant effect in the LH. While ketamine induced a robust place preference, 4-Cl-KYN administration did not induce either place preference or aversion in the conditioned-place preference paradigm, indicating that this drug is neither rewarding nor aversive. Moreover, unlike ketamine, 4-Cl-KYN did not cause a disruption of pre-pulse inhibition. In contrast to ketamine, 4-Cl-KYN administration did not enhance motor activity, locomotor sensitization, or repetitive stereotypic rearing and circling behavior.
Conclusions: These results indicate that administration of a selective antagonist of the NMDA receptor glycineB site produces rapid and long-lasting antidepressant effects in a number of relevant preclinical models, without causing several of the adverse events that are known to be associated with ketamine administration. We are planning a human experimental therapeutic trial with 4-Cl-KYN for the treatment of MDD.
Keywords: Depression, NMDA glycine-site receptor, 4-Chlorokynurenine.
Disclosure: Nothing to Disclose.

W227. Subtypes of Prefrontal Cortical NMDA Receptors in Working Memory and Normal Aging

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Background: Working memory is an executive function subtype characterized as the ability to briefly retain context-specific information. Persistent firing of pyramidal neurons in the prefrontal cortex (PFC), especially during delays interposed between stimulus presentation and response selection, is a likely neurophysiological correlate of working memory. Co-distributed inhibitory interneurons are important for providing specificity in this system. Ionotropic glutamatergic receptors of the NMDA subtype are robustly expressed on both the pyramidal neurons and interneurons within the PFC, and altered activity at these receptors has been implicated in working memory deficits associated with both psychiatric disorders and normal aging. NMDA receptors are biochemically diverse heterotetramers comprised of an obligate NR1 subunit that variously associates with NR2A or NR2B subunits. These specific NMDA receptor subtypes differ in their intrinsic channel properties as well as their relative abundance in PFC pyramidal and interneurons. However, the contribution of these receptor subtypes to working memory deficits is not well understood, especially in the context of normal aging.
Methods: In Experiment 1, young adult male Fischer 344 rats (6 months) were surgically implanted with cannulae directed at the medial PFC (mPFC) and trained to perform a mPFC-dependent delayed response task. After acquisition of stable baseline performance, rats received acute intra-mPFC microinjections of either Ro-25 6981 (1, 3 or 9 μg/hemisphere), a NR2B-preferring antagonist, or NVP-AAM077 (0.3 1 or 3 μg/hemisphere), a NR2A-preferring antagonist. Doses of the drug and vehicle were administered immediately prior to testing in the delayed response task, using a randomized, within-subjects design with a 48 h washout period between successive doses. In Experiment 2, mPFC homogenates were prepared from young (6 month) and aged (22-24 months) Fischer 344 rats. Protein levels of NMDA receptor subunits (NR1, NR2A and NR2B), AMPA receptor subunits (GluR1 and GluR2) and other excitatory synaptic markers (PSD-95 and VGluT1) were quantified using Western blot methods.
Results: In Experiment 1, the NR2B-preferring antagonist produced a significant delay-dependent interaction such that working memory performance was selectively impaired relative to vehicle at long delays (>18 s). The NR2A-preferring antagonist also produced a significant impairment relative to vehicle but there was no interaction with delay. In Experiment 2, Western blot analysis revealed a significant reduction in expression of both the NR1 and NR2A subunits in aged compared to young mPFC and there was a trend towards reduced expression of NR2B. In contrast, expression of GluR1 and GluR2, PSD95 and VGluT1 was comparable in young and aged rat mPFC.
Conclusions: The present experiments demonstrate that blockade of specific subclasses of NMDA receptors produces significant, but distinct, impairments in performance on a rodent mPFC-dependent delayed response task. Moreover, these findings indicate that expression of NMDA receptor subunits is attenuated in the mPFC at an age when working memory deficits are apparent. Jointly, these studies support a role for PFC NMDA receptors in executive function, and further suggest that the decline in NMDA receptor expression may be a causal factor for working memory impairments that are prevalent among older individuals.
Keywords: aging, NMDA receptor, prefrontal cortex, working memory.
Disclosure: Nothing to Disclose.

W228. Chronic Lithium Treatment Attenuates Electrically Evoked and Amphetamine-induced Dopamine Release in the Nucleus Accumbens Core

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Background: Lithium is a mood stabilizer, efficacious in the treatment of bipolar disorder and the reduction of suicidal behavior. Lithium treatment attenuates mania-like behaviors elicited by agents that cause dopaminergic (DA) release in the nucleus accumbens (NAc) in animal models. The clinical efficacy of lithium as a mood stabilizer is well established and its effects on intracellular signaling have been extensively investigated. However the neurobiological mechanisms by which lithium exerts its actions on DA release at the systemic level are not well understood. We used fast-scan cyclic voltammetry (FSCV) to record and analyze changes in extracellular DA concentrations with sub-second temporal resolution in the NAc core evoked by electrical stimulation of the ventral tegmental area (VTA).
Methods: We determined the effects of chronic and acute lithium treatments on DA release. Next, we tested whether chronic lithium had any effect on production or availability of DA by depleting DA with repeated stimulation and release. Finally, we investigated whether lithium attenuated amphetamine induced increases in DA release. Male C57Bl/6J mice were 11-12 weeks old at the start of the experiment. For chronic lithium treatments, mice were fed 0.4% LiCl containing chow or control chow, ad libitum, for 24 to 40 days. For acute lithium treatment LiCl or vehicle were injected prior to making FSCV recordings resulting in brain lithium levels similar to those obtained following chronic administration. A bipolar stimulating electrode was placed in the VTA and a glass-encased carbon fiber electrode was placed in the NAc core. DA release was evoked by trains of 60 rectangular, biphasic pulses (2 ms/phase; 1 pulse train/3 min) delivered to the VTA. While recording at a depth of maximum DA release, a series of eight pulse trains of increasing amplitude was applied to the VTA. Transients evoked by 300 μA pulses were used to assess release and reuptake kinetics. In the DA depletion experiments control or chronically lithium treated mice were given repeated 500 μA stimulus trains of either 20Hz-20 pulses or 60 Hz-60 pulses with 6 second intervals. In the amphetamine experiments, the same depletion stimulus trains were used following an injection of 2mg/kg amphetamine (i.p.) in control or chronically lithium treated mice. Recording electrodes were calibrated after the experiment using a DA solution of known concentration.
Results: Mice treated chronically with lithium had a decreased peak amplitude of stimulation-evoked DA release in the NAc core. There was also a main effect of stimulation amplitude and a significant interaction between the stimulation magnitude and treatment. Mice treated chronically with lithium had significantly lower levels of DA at all stimulation amplitudes from 300 to 700 μA compared to controls. Chronic lithium treatment did not significantly alter the rise time or decay time of the DA transients. Conversely, acute lithium treatment did not significantly alter the peak amplitude or decay constant of stimulus-evoked DA transients. Repeated stimulation revealed that DA release in the lithium group was attenuated in the initial stimulations, however this difference was not evident in further repeated stimulations and both groups had similar depletion curves in 60Hz-60 pulses stimulation. There were no significant differences at any time point in 20 Hz-20 pulses experiments. Chronic lithium treatment attenuated amphetamine induced increases in DA release in both 20 Hz-20 and 60Hz-60 pulse stimulus experiments initially, but not in subsequent stimulations.
Conclusions: Our results demonstrate that chronic (but not acute) lithium treatment attenuates phasic DA release in the NAc core evoked by electrical stimulation of the VTA without altering the kinetics of DA release or reuptake. Since the depletion of DA that we observed was not significantly different between treatment groups, our data also suggest that this difference between chronic lithium treated and control animals was not due to the availability of DA. Finally, we show that lithium attenuates amphetamine induced increases in DA release at the beginning of stimulation, suggesting that lithium's actions are limited to the readily releasable pool of DA, but not the reserve pool. The present results agree with the established clinical finding that lithium treatment is effective only when administered chronically. The amplitude and timing of DA transients in the NAc are critical in reward prediction, motivational and cognitive control of behavior, and impulsivity, which may have relevance to the therapeutic effectiveness of lithium in the treatment of mania and reduction in suicidal behaviors.
Keywords: lithium, dopamine, impulsivity, suicide.
Disclosure: Nothing to Disclose.

W229. The Endogenous Hallucinogen N,N-Dimethyltryptamine and 5-Methoxy-N, N-Dimethyltryptamine Modulate Innate and Adaptive Inflammatory Responses Through the sigma-1 Receptor of Human Dendritic Cells

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Background: The orphan receptor sigma-1 is a transmembrane chaperone protein expressed in both the central nervous system and in immune cells. It has been shown to regulate neuronal differentiation, cell survival, and mediates anti-inflammatory responses and immunosuppressive effects in murine in vivo models. The hallucinogenic N,N-dimethyltryptamine (NN-DMT) is an endogenous ligand of the sigma-1 receptor.
Methods: We studied the effects of NN-DMT, its derivative 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), and the synthetic high affinity sigma-1 receptor agonist PRE-084 on human primary monocyte-derived dendritic cell (moDCs) activation provoked by lipopolysaccharide, polyI:C, or pathogen-derived stimuli to induce inflammatory responses. Gene-specific silencing was used for the confirmation of sigma-1 receptor mediation.
Results: Co-treatment of moDC with these activators and sigma-1 ligands resulted in decreased production of pro-

inflammatory cytokines IL-1β, IL-6, TNFα, and IL-8, while the secretion of the anti-inflammatory cytokine IL-10 was increased. The T-cell activating capacity of moDCs was also inhibited by these ligands, as their combination with E. coli or influenza virus as stimulators indicated decreased differentiation of moDC-induced Th1 and Th17 inflammatory T-cells in a sigma-1 receptor dependent manner as confirmed by gene silencing.
Conclusions: Here we demonstrate for the first time the modulatory effects of NN-DMT and 5-MeO-DMT on immune functions via the sigma-1 receptor. Our findings indicate a biological function of these endogenous compounds which is beyond their hallucinogenic effect.
Keywords: hallucinogens, immunity, inflammation, sigma-1 receptor.
Disclosure: Nothing to Disclose.

W230. Mechanisms of Rotenone-induced the Toxic Aldehyde, DOPAL, Formation from Dopamine in Cultured PC-12 Cells

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Background: Repeated administration to rats of rotenone, an inhibitor of mitochondrial complex I, has been shown to deplete striatal dopamine (DA) and promote intra-neuronal deposition of alpha-synuclein, which are hallmarks of Parkinson's disease (PD) in humans. In PD, postmortem levels of dihydroxyphenylacetaldehyde (DOPAL) are increased, apparently as a result of diminished aldehyde dehydrogenase (ALDH) and enhanced formation of the aldehyde as a result of diminished efficiency of vesicular DA sequestration. In this study we sought to determine if similar abnormalities can be demonstrated in cultures of PC12 cells exposed to rotenone.
Methods: Cultured PC 12 cells were trypsinized, suspended in media, counted, and diluted with medium to provide 200,000 cell/ml. One ml of these suspensions was transferred to each well and after 48 hours, the medium was removed and replaced with 1 mL of the same medium containing 10 μM tolcapone to inhibit catechol-O-methyltransferase. The incubation was continued until the next day when rotenone was added to the medium in amounts that resulted in a range of concentrations (10-1000 nM). After 24 hours, tubes were centrifuged, the media were removed and the sedimented cells were taken up into 400 μl of a phosphoric and acetic acids. Samples of the media and the solubilized cells were frozen until assayed for catechols. In anther experiment, the time course of the changes in media and cell contents of endogenous catechols were determined at 10, 20, 30, 60, 120 and 180 minutes after incubation in media containing 100 mM rotenone. In a third study, PC 12 cells that had been preinccubated for 24 hours in medium containing 10 μM tolcapone were incubated with 1-2 μM 6-fluoro-DA (F-DA) with 10-1,000 nM rotenone. After 3 hours, the cells were separated from the media, taken up into 400 μl acid acid as described above. Both the cell solutions and media were frozen at until assayed for endogenous and fluorinated catechols. Assays of endogenous and fluorinated catechols were assayed by HPLC and electrochemical detection after alumina extraction by methods previously described from our laboratory.
Results: After incubation for 24 hours with concentrations between 10 and 100 nM rotenone, dopamine content of the cells was only slightly lower than baseline, but there were dose-related increments in dopamine content of the media. At the lowest rotenone concentration, media dopamine accounted for less than 10% of the total dopamine in the cells and media and at the highest concentration of rotenone the media contained about 30% of the total dopamine. In contrast with dopamine, almost all of its deaminated products were found in the media. The media contained 98-99% of both DOPAL and DOPET at 0-1000 nM of rotenone. The levels of DOPAL and DOPET were dose-related between 5 and 100 nM but did not increase further at higher rotenone concentrations. At all rotenone concentrations, cell contents of the catechols paralleled the much higher concentrations in the media. DOPAC levels in the media and in the cells peaked at a rotenone concentration of 50 nM, but fell markedly at 100 nM, consistent with inhibition of aldehyde dehydrogenase. This was most evident in the fall in the ratio of concentrations of DOPAC to DOPAL. Without rotenone, DOPAC accounted for about 2/3 0f the deaminated dopamine metabolites, whereas when rotenone was present, the percentage fell to about 10% while DOPET rose from about 30% to 70% of the dominated metabolites. During the 3 hour incubation of PC12 cells in media containing 100 nM rotenone there was a time dependent linear increases in DOPAL, DOPAC, DOPET, and DHPG, whereas levels of dopamine and norepinephrine were unchanged. Experiments in which fluordopamine (F-DA) was added to the incubation media showed that rotenone diminished amine uptake into the cells, resulting in higher media content of the amine and decreased F-DOPAC formation while increasing the very low levels of F-DOPAL in the media.
Conclusions: The primary effect of rotenone is blockade of mitochondrial Complex I, which is required for conversion of NADH to NAD + and subsequent formation of ATP. These deficits affect oxidative processes and energy requiring transport systems. The various effects of rotenone on the transport and metabolism of catecholamines may be explained by the consequences of its primary effect. Aldehyde dehydrogenases are NAD + dependent enzymes and cannot function properly if formation of NAD + from NADH is blocked rotenone. Monoamine oxidase A, which belongs to the family of flavin-containing amine oxidoreductases, can continue to function since these enzymes do not require NAD + . Thus, rotenone does not affect the deamination of DA or F-DA to their respective aldehydes. In addition to its effect on aldehyde dehydrogenase, the rotenone induced diminished energy metabolism appears to limit active amine transport at both the cell and vesicular membranes. Thus, uptake of F-DA into the PC12 cells was diminished by rotenone and the partial blockade of the vesicular uptake resulted in a shift in the disposition of dopamine from vesicular storage to deamination to DOPAL. The combined effects on Complex I inhibition and effects of cytoplasmic catechol aldehydes, e.g., protein aggregation and autoxidation participate in a viscious circle leading the selective vulnerablity of catecho-

laminergic neurons to degeneration in PD and related disorders.
Keywords: Rotenone, Dopamine, Aldehyde, Parkinson.
Disclosure: Nothing to Disclose.

W231. Synaptic Mechanisms of Ethanol-induced Disinhibition of the Mouse Dorsolateral Striatum

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Background: An intact dorsolateral subregion of the striatum (DLS) and endocannabinoid (eCB) signaling through the cannabinoid receptor 1 (CB1) are necessary for habitual action formation (Hilário and Costa, 2008). As such, the DLS represents a key point of perturbation for drugs of abuse, including ethanol. A recent study in a chronic ethanol drinking model in macaque monkeys demonstrated that GABAergic transmission onto the principal medium spiny projection neurons (MSNs) in the putamen/DLS is depressed relative to control animals, suggesting that excessive, habitual use of ethanol may, in part, arise from a disinhibition of the DLS (Cuzon Carlson et al., 2011). However, little is known about the mechanisms leading to this effect and how the eCB system may be involved. MSNs, the output neurons of the striatum, are potently inhibited by the GABAergic parvalbumin-expressing fast-spiking interneurons (FSIs), which densely populate the DLS and heavily express CB1.
Methods: To test the ethanol effects on FSI-MSN synaptic transmission, we have injected a virus that expresses channelrhodopsin 2 and the fluorescent protein mCherry only in the presence of cre recombinase into the striatum of mice expressing cre under the control of the parvalbumin promoter. Brief (4 ms) exposure of blue light (473 nm) to striatal slices from these animals elicits single action potentials in FSIs and single inhibitory postsynaptic currents (IPSC) in MSNs. IPSC amplitudes were averaged per minute, expressed as percentage of average baseline amplitude, and compared using a two-tailed Student's t test.
Results: We find that acute ethanol (50 mM) induces the postsynaptic release of an opioid in a calcium and SNAP-25-dependent manner to activate a previously unrecognized, presynaptically-localized delta opioid receptor (DOR). Ethanol-induced opioid release and subsequent DOR activation results in a long-term depression (LTD) of FSI-MSN synaptic transmission we term DOR-LTD. Examining the interaction between this ethanol-induced DOR-LTD and the eCB-mediated LTD (eCB-LTD) that we previously discovered at this synapse, we find that DOR-LTD and eCB-LTD are mutually occlusive.
Conclusions: Given the necessity of striatal eCB signaling for habit formation and the present finding of a direct interaction between eCB-LTD and DOR-LTD suggest that this ethanol hijacking of normal eCB control of the FSI-MSN synapse contributes to the striatal disinhibition that fosters habitual drinking. As such, these data suggest that targeting DOR may be a possible strategy for therapeutic intervention in alcohol abuse disorders.
Keywords: basal ganglia, GABA, addiction, plasticity.
Disclosure: Nothing to Disclose.

W232. Dynorphin Controls the Gain of an Amygdalar Anxiety Circuit

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Background: The Bed Nucleus of the Stria Terminalis (BNST) plays a key role in regulation of stress and addiction related behavior. Kappa opioid receptors (KORs) and their endogenous ligand dynorphin are located throughout the brain, including the BNST, and modulate aversive or anxiogenic related behaviors. However, the relationship between the dynorphin-KOR system and BNST function and behavior is unknown.
Methods: We used a multi-facetted approach to probe the ability of the BNST dynorphin-KOR system to modulate circuit function and anxiety-related behavior. In order to define and mechanistically probe how KOR modulate neuronal function in the BNST, we used whole-cell slice electrophysiology. We then utilized optogenetic approaches combined with slice physiology to probe circuit specific actions of KOR. Then, in order to determine how endogenous dynorphin could influence circuit function, we used optogenetic approaches with a dynorphin-cre driver line. We then used in vivo optogenetics combined with pharmacological approaches to dissect how manipulation of this circuit could influence anxiety-like behaviors. Finally, we assessed how stress alters this circuit using a combination of optogenetics and reporter mice.
Results: We found, using whole-cell electrophysiology recordings, that KOR activation inhibited glutamate inputs from the basolateral amygdala (BLA), but not the prefrontal cortex (PFC), demonstrating pathway specificity of KOR modulation. Further, using converging approaches, we demonstrated a presynaptic locus of function of this effect. We then found that this form of KOR modulation was p38 MAP kinase and calcium-dependent. In a series of parallel experiments, we examined the nature of these changes and their relationship to KOR-dependent changes in anxiety-like behavior. We transfected the BLA with an AAV encoding a CamKii-driven ChR2, and implanted an optical fiber above the dorsolateral BNST. We found that light-activation of the BLA-BNST pathway produces an anxiolytic effect in multiple assays, and that this phenotype is blocked by administration of a KOR agonist. We next investigated the potential source of dynorphin to the BNST using a combination of anatomy and electrophysiology. Our results indicate that KOR dependent modulation of glutamatergic transmission in the BNST is due primarily to dynorphin release from local neurons in the BNST.
Conclusions: Taken together, this data supports the conceptual model that dynorphin released from BNST neurons activates KOR on BLA inputs to the BNST act to enhance anxiety by suppressing glutamate transmission.
Keywords: Amygdala, Dynorphin, Anxiety, Circuit.
Disclosure: Nothing to Disclose.

W233. Regulation of Prefrontal Cortex Activity by VTA Dopamine Terminals Following Chronic Cocaine Self-administration & Cue-reinstatement: An Electrophysiological Analysis Using Optogenetics & DREADDs

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Background: Under normal conditions, dopamine (DA) release in the prefrontal cortex (PFC) mediates multiple cognitive processes, including the gating of sensory information. Under pathological conditions such as addiction, executive function is disrupted, the PFC becomes hyper-responsive to drug-associated cues, and cortical DA takes on a permissive role in the reinstatement process. Precisely how DA functions at the cellular level and why the cortex becomes hyper-responsive in addiction remains unclear. To better understand this relationship, first we performed whole-cell patch clamp recordings of pyramidal cells in brain slices from naïve animals while selectively recruiting VTA terminals expressing either opsins (ChR2) or synthetic Gq and Gs-coupled DREADDs (Designer Receptors Exclusively Activated by Designer Drugs). Additional experiments were performed then in tissue from animals with a history of cocaine self-administration with extinction plus cue-reinstatement, yoked-cocaine exposure, or sucrose self-administration with extinction. We observed that VTA DA terminals normally regulate a D1-dependent inhibitory mechanism in PFC neurons. However after operant exposure to cocaine with cues, this form of inhibition shows an enduring adaptation that results in hyperexcitability. This adaptation is not observed in yoked-cocaine or sucrose self-administration animals.
Methods: Cre-dependent AAVs were injected into the VTA of TH-Cre rats to selectively transfect VTA DA cells with channel rhodopsin (ChR2) or synthetic receptors (DREADDs). After ~30d, PFC brain slices were prepared. Whole cell patch clamp recordings were performed in L5 pyramidal cells and VTA terminals were stimulated with transient pulses of blue light (to activate ChR2) or bath application of CNO (to activate DREADDs).
Results: Under baseline conditions, cells displayed robust spike-frequency adaptation (accommodation) and a large slow after-hyperpolarization (sAHP). Activation of ChR2 or DREADDs reduced the sAHP, reduced accommodation, and increased firing. Co-application of cocaine increased the percentage of responsive cells, but not the magnitude of firing. Similar changes were observed with bath application of DA, the D1 agonist SKF81297, direct activation of cyclase activity with forskolin, or depletion of intracellular $Ca2+$ stores with CPA. To evaluate this mechanism in a model of addiction, similar recordings were made in slices from animals with a history of chronic cocaine self-administration. Under these conditions, cells demonstrated (a priori) a compromised sAHP and accommodation, as well as hyperexcitable firing rates. Acute blockade of DA-D1 receptors, inhibition of PKA, or depletion of intracellular $Ca2+$ restored accommodation following chronic cocaine self-administration. As KCNQ (Kv7) $K+$ channels mediate accommodation and play a role in the AHP, we compared KCNQ channel function in cocaine-experienced tissue to controls. In controls, blockade of KCNQ channels with XE991 eliminated accommodation. Following chronic cocaine self-administration, stabilization of KCNQ channel function with retigabine restored accommodation. In voltage clamp, KCNQ channel currents from cocaine experienced animals showed reduced activation in response to depolarizing steps—an adaptation normalized by retigabine, or blockade of PKA with H-89, or depletion of intracellular $Ca2+$ stores with CPA. Ongoing experiments test the hypothesis that following chronic cocaine self-administration changes in PKA and intracellular $Ca2+$ signaling shift the activation potential of KCNQ channels.
Conclusions: Taken together these data suggest that VTA terminals utilize a DA-D1 receptor mechanism to regulate PFC excitability. In the transition from acute exposure to chronic cocaine self-administration and extinction, this mechanism becomes superactivated, resulting in a reduced sAHP and KCNQ channel mediated inhibition. This neuroadaptation may underlie the enhanced saliency of drug-related cues that trigger relapse in cocaine addicts.
Keywords: prefrontal cortex, dopamine, Ventral tegmental area (VTA), addiction.
Disclosure: Nothing to Disclose.

W234. The Indirect Pathway is Not What You Think: D1 Medium Spiny Neurons Input to the Ventral Pallidum is Involved in Cocaine Addiction

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Background: The nucleus accumbens (NAc) serves as the input structure of the basal ganglia and is central to addictive behavior. Information entering the NAc is processed and then sent to output structures of the basal ganglia (such as the substantia nigra (SN) and the ventral tegmental area (VTA)) in two parallel pathways: a direct pathway that consists of medium spiny neurons (MSNs) directly innervating the output structures and an indirect pathway, in which the striatal axons first innervate the ventral pallidum (VP), which then sends axons to the output structures. The direct pathway is classically considered to consist solely of MSNs expressing the D1-dopamine receptor (D1-MSNs), while the indirect pathway consists solely of MSNs expressing the D2-dopamine receptor (D2-MSNs).
Methods: We used whole-cell patch clamp electrophysiology to test whether the widely accepted division of D1- and D2-MSNs into direct and indirect pathways is accurate and to examine whether these inputs are differentially changed after extinction of cocaine self-administration. For the latter experiment, mice self-administered cocaine (or saline) for 14 days followed by ~14 days of extinction. Slices were prepared 24 hours after last day of extinction. To achieve specificity in D1- or D2-MSN activation we microinjected Cre-dependent channelrhodopsin (ChR2) into the NAc core (NAcore) of D1- or D2-Cre mice and activated those inputs optogenetically. To achieve specificity in projection neurons

in the VP we microinjected retrobeads into the VTA/SN and recorded from retrogradely-labeled VP neurons.
Results: We found that ~50% of VP cells were innervated by D1-MSNs while almost all VP cells were innervated by D2-MSNs. In contrast, cells in the SN received only D1-MSN input from the NAc, while the globus pallidus received almost exclusively D2-MSN input from the dorsal striatum. To examine the possibility that accumbens D1-MSNs form an indirect pathway through the VP we optogenetically activated D1-MSN terminals in the VP while recording from VP cells retrogradely labeled from the VTA/SN. We found that a substantial proportion of VTA/SN-projecting VP neurons received input from D1-MSNs. Lastly, we examined whether the D1-MSN and D2-MSN inputs to the VP change after extinction of cocaine self-administration. We found that while long-term depression (LTD) could be induced in both inputs in yoked saline mice, LTD could not be induced in D2-MSN input to the VP in cocaine-extinguished mice but was still present in D1-MSN input.
Conclusions: Our results call for a revision of the current view of the direct and indirect pathways of the ventral striatum, with emphasis on the VP as an integration point of the majority of the NAc output. Our preliminary data suggests that the D1-MSN and D2-MSN inputs to the VP may have a differential and equally important role in addiction, but further examination of these projections is required to determine the behavioral importance of the D2-MSN and the newly discovered D1-MSN input to the VP.
Keywords: Ventral Pallidum, Nucleus Accumbens, Electrophysiology, Direct pathway.
Disclosure: Nothing to Disclose.

W235. Inflammation and Fatty Acids in Bipolar Disorder: A Dietary Treatment Link

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Background: The omega (n)-3 polyunsaturated fatty acid (PUFA) docosahexaenoic acid (DHA) and the omega-6 PUFA arachidonic acid (AA) comprise over 90% of nutritionally essential fatty acids in brain phospholipids, and are derived from both diet and from synthesis in the liver from precursors, alpha-linolenic acid (ALA) and linoleic acid (LA), respectively. Recent post-mortem studies link upregulation of brain AA metabolism to inflammatory products that worsen bipolar disorder (BD), an epidemiological study indicated that the NSAID aspirin reduced morbidity in patients taking lithium, and preclinical studies in rats indicated that mood stabilizers effective in BD downregulate brain AA metabolism. Additionally, an epidemiological study reported reduced prevalence of BD in subjects having a high DHA-containing fish diet.
Methods: We report an observational, parallel group study designed to compare PUFA biomarkers between symptomatic BD (N = 30) patients before treatment and after symptomatic recovery, and healthy controls (HC) (N = 31). Patients were recruited from clinical settings, and were in depressed (N = 12), manic (N = 6), or mixed (N = 12) states. After naturalistic treatment, participants had levels of manic symptoms below threshold for symptomatic recovery, with depressive symptoms in the mild range for the baseline depressed and mixed groups.
Results: Measurements of plasma biomarkers at baseline showed a lower ratio of bound (unesterified):free(esterified) ALA ($p = 0.04$) in symptomatic BD (N = 18) than in HC (N = 18), and a higher ratio of free DHA:ALA ($p = 0.02$) in BD than HC. Both findings point to less ALA available for conversion to eicosapentaenoic acid (EPA) or DHA, a precursor to anti-inflammatory products. In addition, mania scores were negatively correlated with levels of AA ($p = 0.01$) and free:bound AA ($p = 0.05$). Data from the full sample of this trial will be presented.
Conclusions: A pro-inflammatory metabolite of AA, prostaglandin E2, has been implicated in many pain syndromes, including migraine headache. Migraine overlaps with BD in clinical co-morbidity, epidemiology and treatment. Our large observational longitudinal study found a 6-fold increase in migraine in BD over healthy controls, associated with earlier age at onset, more severe and frequent depression over follow-up in the patients. Overlap in pathophysiology and treatments in BD and migraine suggests that dietary interventions involving PUFAs may be useful for both disorders. Indeed, a 12-week randomized trial comparing effects of a high EPA + DHA plus low omega-6 (H3-L6) dietary intervention to an intervention that only lowered omega-6 PUFA in 67 patients with chronic headaches showed clinical improvement in both groups, but the H3-L6 group experienced significantly greater reduction in headaches, quality-of-life and psychological distress. Based on the clinical and neuroinflammatory link between BD and migraine, we will outline a funded protocol to test if H3-L6 dietary intervention would be effective as an adjunct treatment of bipolar disorder.
Keywords: bipolar, omega-3, biomarkers, inflammation.
Disclosure: Alan Gelenberg: Consultant for Zynx Health, Allergan; stock in Healthcare Technology Systems, Inc.; Erika Saunders: Consultant for Projects in Knowledge, Inc.

W236. Brain State-Dependent Abnormal LFP Activity in the Auditory Cortex of a Schizophrenia Mouse Model

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Background: Neural oscillation and synchronization abnormalities have been suggested to play a role in the information and sensory processing deficits commonly seen in schizophrenia. Periodic auditory stimulation entrains EEG to a specific phase and frequency, often referred to as the auditory steady-state response (ASSR). In schizophrenia, reduced ASSR power (magnitude) and phase locking (phase consistency across trials), particularly at 40 Hz, are observed in EEG & MEG studies, by assessing stimulus-evoked responses in synchrony compared with a pre-stimulus spontaneous baseline. However, the evidence regarding baseline gamma band abnormalities is incon-

sistent. To measure the baseline spontaneous power with high precision, it would be useful to directly record local field potentials (LFPs), necessitating the use of animal models. To that end, we recorded LFPs directly from the primary auditory (A1) cortex of interneuron-specific NMDA receptor deletion mice to assess the click train-evoked ASSRs and baseline LFP fluctuations.

Methods: The microwire array was inserted into the A1 cortex superficial layers of Ppp1r2-cre(+ /-)/fGluN1(f/f) mutant mice and their floxed-controls (12-16 week old) under anesthesia, and was fixed after single-tone evoked potentials (over 0.1 mV) were detected. Seven days after the surgery, LFP recording was performed from A1 cortex of awake, head-restrained mice. In the first session, spontaneous LFP activity during a pre-stimulus period was recorded from A1 cortex. In the 2nd session, 500-ms long click trains consisting of 80 dB white-noise pulses presented at 40 Hz (40-Hz ASSR stimuli) were applied 50 times with an inter-stimulus interval of 20 sec, which mimics the ASSR protocol used in human studies (Krishnan et al, 2009). Auditory click stimuli, consisting of white noise pulses (1 ms, duration; 80 dB, SPL), were generated in Labview, and presented using a speaker above the mouse head. In the 3rd session, which began 10 min after cessation of the second session, 1000-ms long click trains consisting of 80 dB white-noise presented at 20 Hz (20-Hz ASSR stimuli) were applied 50 times with an inter-stimulus interval of 20 sec. In the last session, spontaneous LFP activity was recording for 25 min as a post-stimulus period. To assess the evoked ASSRs, z-score normalized LFPs during the last 200-ms of each ASSR were analyzed with a fast Fourier transform (FFT) algorithm in the range of 0–100 Hz using 256 frequency bins and presented as ASSR power. For spontaneous LFPs, LFP data (200-ms bin) during the last 10 sec prior to the first click-train administration, from 5 sec to 15 sec (200-ms bin) after 1st stimuli, 25th stimuli and 50th stimuli, and from a 10-sec period (200-ms bin) 20 min after the cessation of all ASSR stimuli were analyzed with FFT algorithm in the range of 0-200 Hz.

Results: Seven days after surgery, 40-Hz click train-evoked initial N1 responses (the transient auditory evoked potentials to click train onset) were robustly evoked within the first 100 ms after click-train onset in the A1 cortex from 7 floxed-GluN1 control and 6 mutant mice. There was no difference in the averaged N1 amplitudes between genotypes per animal. However, the amplitudes of 40-Hz ASSRs were smaller in the mutants compared to the controls per animal and per channel. Also, phase locking at 40 Hz in the mutants was lower in comparison to controls. These findings suggest that mutants are severely impaired in 40-Hz ASSR for both amplitude and phase locking, both of which are reminiscent of ASSR deficits in schizophrenia patients. Both ASSR and phase-locking evoked by 20-Hz ASSR stimuli are also diminished in the mutants. We explored the levels of spontaneous power throughout the periods of pre-, inter-ASSR and the post-ASSR period, and found baseline spontaneous power during the last 10-sec pre-stimulus period prior to the first click-train administration was augmented in the mutants compared to the controls regardless of the spectral frequency. After the 40-Hz ASSR session began, a clear trend of a gradual reduction in mutant spontaneous LFP power amplitudes appeared during inter-stimulus intervals with the increasing number of ASSR stimuli. Consequently, no genotypic difference was detected in spontaneous LFP power magnitudes during 10-sec inter-stimulus intervals (combined data of first, 25th and 50th ISIs) at any power spectra examined. Interestingly, 20-min after the last ASSR, the spontaneous LFP power in the mutants appeared to increase back to the abnormally high level of pre-stimulus period. These results suggest brain state-dependent abnormality of baseline spontaneous LFP power in the mutant mice; an abnormally high spontaneous LFP power in an awake quiescent period, which disappears upon receiving external auditory stimuli. It appears that the evoked ASSR deficit found in our mutants is not due to greater baseline spontaneous gamma power, rather it is simply caused by the deficits in evoking responses by external stimuli.

Conclusions: In addition to click trains-evoked ASSR deficits at 40 Hz, we observed in the mutants that the broadband elevation of spontaneous LFP power in the pre-stimulus period disappeared during the inter-ASSR stimulus periods. A1 cortex superficial pyramidal cells and fast-spiking neurons generate "synchronous state" in awake quiescent period, and their coordinated activity is largely suppressed during auditory stimuli-induced cortical desynchronization (Sakata and Harris, 2012). Considering that the majority of cell-types in which NMDAR elimination occurred in our mutant mice are PV-positive fast-spiking neurons, it is conceivable that the state-dependent elevation of spontaneous LFP power reflects the dysfunction of mutant cortex fast-spiking neurons to be more engaged during awake quiescent period. This phenotype is remarkably similar to a clinical report of "paradoxical" engagement of A1 cortex of schizophrenia patients, such that left A1 cortex displays increased activation in the absence of external auditory stimuli (but with auditory verbal hallucinations), and decreased activation when an external stimulus was actually present (Kompus et al., 2011).

Keywords: gamma oscillation, NMDA receptors, schizophrenia, GABAergic interneurons.

Disclosure: Nothing to Disclose.

W237. Phasic Dopamine Differentially Encodes Appetitive and Consummatory Aspects of Food Reward

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Background: Rewards, and reward-predictive cues, evoke brief (phasic) increases in extracellular dopamine that are critical for associative learning. The development of these signals during learning has been studied using Pavlovian conditioning paradigms, which typically involve a food reward (sugar pellet or solution) being delivered several seconds after an environmental cue. However, in most studies of this kind subjects are required to collect the reward from a receptacle. Therefore, it is unclear to what extent the observed patterns of dopamine signaling reflect appetitive processes involved in reward collection such as motor generation. Here, to address this uncertainty, we

compared dopamine responses evoked by sucrose pellets and pellet-predictive cues to responses evoked by intraoral infusions of an equivalent amount of sucrose and infusion-predictive cues. Importantly, whereas pellets required both appetitive and consummatory actions, intraoral infusions isolated the consummatory phase.
Methods: Rats were trained for seven days in a Pavlovian paradigm consisting of interleaved trials (25 per reward) in which each type of reward (45 mg sucrose pellet vs. 0.33 mL of 0.4 M sucrose solution) was preceded by a distinct compound cue (3 s right or left light/lever, counter-balanced). After training, rats experienced a single test session consisting of cue/reward trials, as in training, as well as probe trials, in which each reward was delivered in the absence of cues. During this test session, phasic dopamine in nucleus accumbens (NAc) core or shell was recorded using fast scan cyclic voltammetry.
Results: Rats made more entries into the food cup after presentation of the pellet-paired cue, relative to the infusion-paired cue, demonstrating discrimination between cues. Despite this behavioral difference, robust dopamine spikes of similar magnitude were seen in response to both cues that predicted pellets and cues that predicted infusions. In contrast, at time of reward delivery, dopamine responses were only observed in response to pellets and not in response to infusions. In probe trials, when rewards were unpredicted, dopamine responses were evoked by pellet delivery but the response to infusions differed according to NAc subregion. As such, no response was seen in NAc core whereas a sustained dopamine response was seen in NAc shell. In addition, in all trials, responses in shell had a longer decay than responses in the core, perhaps reflective of differences in release dynamics and/or rate of dopamine reuptake between the regions.
Conclusions: Determining how the brain encodes and processes rewards and other environmental stimuli is essential for understanding how reward-based learning occurs. Here, we show that certain neural signals believed to be evoked by reward receipt can actually be attributed to other task features, primarily reward prediction. This work has implications for all behaviors involving learning about rewards including pathological states of reward dysfunction such as drug addiction and forms of obesity.
Keywords: dopamine, Pavlovian, associative learning, cues.
Disclosure: Nothing to Disclose.

W238. Examining Working Memory Evoked Gamma Oscillations in Cannabis Dependent Patients with Schizophrenia and Non-psychiatric Controls

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Background: Cannabis dependence among patients with schizophrenia represents a significant co-morbidity resulting in the worsening of positive and negative symptoms, however, the effects on cognition are unclear. Working memory represents a core deficit in patients with schizophrenia in which previous studies report both superior and worse performance with cannabis use. It is possible that cannabis use may modulate gamma (30-50 Hz) oscillations in the dorsolateral prefrontal cortex (DLPFC) that mediate working memory. The aim of this study was to evaluate working memory performance and gamma oscillations while cannabis dependent patients and controls perform the verbal N-Back task.
Methods: In an on-going study examining the long-term abstinence effects of cannabis on working memory evoked gamma oscillations, we have tested 8 (mean age 30.2 ± 10.2 years) medicated patients with schizophrenia and 7 (mean age 26.1 ± 3.4 years) non-psychiatric controls. All subjects were male. The verbal N-back task administered at the 1- and 3-back working memory load while electroencephalography (EEG) was collected with a 64-electrode cap and DC-coupled EEG system at 1000 Hz with a 0.3 to 200 bandpass filter. EEG data was processed offline using MATLAB 7.04 (The Mathworks, Inc. Natick, MA, USA) and the EEGLAB toolbox. Gamma oscillatory activity was measured from the frontal electrodes (AF3/4, F1/2, F3/4, F5/6, and F7/8) encompassing the DLPFC for correct responses to targets. EEG signals were filtered into the gamma (30-50 Hz) frequency band with a zero-phase shift and then Hilbert transformed to separate phase and amplitude of the signal. Gamma power was calculated and averaged across the entire epoch from -1000 to 3095 relative to stimulus onset.
Results: N-Back accuracy was similar among groups demonstrating poorer performance on the 3-Back compared to the 1-Back ($p = 0.001$; Cohen's $d = 0.95$) working memory load. No significant differences were found in working memory evoked gamma oscillations. Significant negative relationships were found between increased gamma oscillations and N-Back accuracy across all subjects (1-Back: $r = -0.671$, $p = 0.006$; 3-Back: $r = -0.595$, $p = 0.019$). Among patients, this relationship was observed in the 1-Back ($r = -0.767$, $p = 0.027$), but not in the 3-Back; while in controls the relationship was preserved in both working memory loads (1-Back: $r = -0.782$, $p = 0.038$; 3-Back: $r = -0.780$, $p = 0.038$).
Conclusions: Preliminary findings suggest that increased gamma oscillations may be related to poorer performance in cannabis dependent controls. By contrast, patients may employ complementary or different mechanisms to solve the 3-Back working memory load such as, theta-gamma coupling. Additional subjects will help to uncover this relationship and possible differences in gamma or theta-gamma coupling that are hypothesized to mediate working memory. Given that cognitive deficits serve as a predictor of long-term functional outcome, understanding the role of cannabis on working memory may help to guide future treatments for this common and significant co-morbidity.
Supported in part by NARSAD Young Investigator Grant to Dr. Barr and a Canadian Institute of Health Research (CIHR) operating grant MOP#115145 to Dr. George.
Keywords: Schizophrenia, Cannabis Dependence, Gamma Oscillations, Working Memory.
Disclosure: Dr. Zafiris J. Daskalakis (Part 1: Roche Advisory Committee; Part 4: Brainsway Inc. Operational Grant). Dr. Tony P. George (Part 1: Consulting fees from Novartis; Part 4: Pfizer Investigator Initiated Research Grant). Dr. Mera S. Barr, Ms. Michelle S. Goodman and Ms. Rachel A. Rabin have no relevant financial interests to disclose.

W239. Increased beta-gamma Power Ratio in MEG Auditory Steady-state Responses: A Potential Biomarker for Chronic Schizophrenia

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Background: Rhythmic activity plays a critical role in the function of the brain. Disruption of normal timing of neural events may underlie the diverse neurocognitive deficits in a number of neuropsychiatric disorders. In the past decade, a large amount of evidence for abnormalities in neural timing, as mediated by oscillatory activity, has emerged in studies of schizophrenia. The most robust deficit identified so far is the disruption of the auditory steady-state response (ASSR) in patients with chronic schizophrenia in EEG studies, particularly at a stimulation periodicity of 40 Hz (gamma frequency). Differences in healthy and schizophrenia subjects for response frequencies other than 40 Hz, however, have been inconsistent across studies. For example, there is some evidence for an increase in the ASSR for 20 Hz (beta frequency) stimulation among schizophrenia patients, but differences in these studies did not consistently reach statistical significance. The objectives of the work described here are first, to quantify and lateralize the ASSR for multiple stimulation and response frequencies in schizophrenia using magnetoencephalography (MEG) and source analysis in the auditory cortex; and second, to determine if any of the metrics or combinations of metrics derived may constitute a potential biomarker for the illness.
Methods: Thirteen medicated chronic schizophrenic subjects and thirteen age-matched healthy control subjects were recruited through an academic medical center in the Boston metropolitan area. Eleven subjects were taking second generation (atypical) antipsychotics, and two were taking first generation antipsychotics. To instantiate the ASSR task, approximately 500 ms duration click trains were presented bilaterally at 65dB SL while a 306-channel magnetoencephalogram was recorded. Stimulation of clicks was at 20Hz, 30Hz, and 40Hz with at least 100 stimuli per type. Equivalent current dipoles were fitted to the late magnetic field (comprising the steady-state response). Spectral power was calculated using the grand averaged waveforms from a two-dipole model, which localized in or near Heschl's gyrus bilaterally, using a single layer boundary element model (BEM). For statistical analysis, four separate two-way ANOVAs were run, each of the form Power = Hemisphere + Group + Hemisphere x Group, where the two groups were schizophrenic patients vs. healthy controls, and hemisphere corresponded to the right vs. left dipolar current estimates. Outcome measure (power) for the separate cases were 20 Hz response to 20 Hz stimulation, 30 Hz response to 30 Hz stimulation, 40 Hz response to 40 Hz stimulation, and 20 Hz response to 40 Hz stimulation.
Results: In subjects with schizophrenia, the spectral power of the 20 Hz response was significantly increased with 20 Hz stimulation ($F = 4.79$, $p = .034$). Similarly, for 20 Hz response to 40 Hz drive, patients showed significantly greater power than controls ($F = 9.64$, $p = .003$). In neither case was there a significant hemisphere effect or group x hemisphere interaction. For 30 Hz activity, no significant effects were seen. For 40 Hz response to 40 Hz drive, schizophrenics showed decreased power as compared with controls, but this did not reach statistical significance; there was a hemisphere main effect ($R > L$) ($F = 10.44$, $p = .002$). Of note, a sensitive marker for distinguishing the schizophrenia group from the control group was the ratio of the spectral power of the response at 20 Hz to the response at 40 Hz, in response to 40 Hz drive ($t[24] = -2.63$, $p = .015$). For this measure, receiver operator characteristics (ROC) analysis showed an area under the curve of .775 ($p = .017$), indicating the beta-gamma ratio significantly differentiated schizophrenics from control subjects; this metric showed relatively high sensitivity (.769) and specificity (.692).
Conclusions: Here we show that the auditory cortex in schizophrenia exhibits greater responsiveness at 20 Hz in comparison to controls, both in response to 20 Hz and 40 Hz drive. Significantly, we also found that patients showed an increased beta-gamma power ratio; this, to our knowledge, has not been previously demonstrated. The significance of this work is twofold. First, these findings support an intrinsic defect in schizophrenic patients' auditory cortex, which may lead to dysfunctions such as hallucinations. In conjunction with a substantial body of recent literature suggesting rhythmic brain activity depends on a precise interplay between GABAergic and glutamatergic neurons, our work suggests a mechanistically plausible connection between the putative neurobiology of schizophrenia and clinically observable phenomena. Second, the beta-gamma ratio may represent a metric that can differentiate controls from schizophrenic patients; this could be confirmed in future ASSR studies, or by reanalysis of data from existing ones. This would represent a biomarker of high potential utility, both for clinical purposes, and in animal and computational models of the illness.
Keywords: magnetoencephalography, gamma oscillations, beta oscillations, biomarker.
Disclosure: Steven Stufflebeam: Has served as consultant for, and received travel funds from, Elelekta-Neuromag (maker of MEG equipment).

W240. Physical Activity and Heart Rate Variability in HIV Infection and Methamphetamine Dependence

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Background: Physical activity (PA) provides significant benefits and has been proposed as a non-pharmacological intervention to improve health in HIV-infected (HIV+) individuals and persons with substance dependence. However, knowledge about everyday PA in people with HIV and adults with methamphetamine (METH) dependence remains limited. PA is also demonstrated to improve autonomic nervous system (ANS) function, which is

impaired in both HIV and METH dependence, although the combined effect of these factors on ANS activity is unknown. We hypothesized that HIV + subjects with comorbid METH dependence (METH +) would exhibit reduced PA and impaired ANS function as evidenced by reduced heart rate variability (HRV) relative to participants with either HIV or METH dependence alone. Further, we proposed that participants with higher PA would exhibit higher HRV compared to less active participants.
Methods: A total of 127 participants were evaluated, including 44 HIV-/METH-, 26 HIV + /METH-, 35 HIV-/METH + , and 22 HIV + /METH + individuals. We recorded HRV during a 5-minute rest period with the Equivital EQ01 Life Monitor, an ambulatory device with a two-lead electrocardiogram sensor. HRV data were analyzed using time domain, frequency domain, and nonlinear measures, including the root mean square of successive RR differences (RMSSD), the low frequency/high frequency (LF/HF) ratio, and Poincare plot SD1 and SD2. PA was assessed with the International Physical Activity Questionnaire (IPAQ), a self-report form that records the quantity of vigorous and moderate PA, walking, and sitting over the previous 7 days.
Results: HIV + participants exhibited significantly reduced RMSSD and SD1 compared to HIV- participants ($p < 0.05$), while METH + participants with heavy lifetime exposure (> 1000 days of use) also exhibited worse HRV relative to individuals with fewer days of METH use ($p < 0.01$). HIV-/METH + participants reported higher walking relative to other groups and HIV + participants indicated more sitting on the IPAQ compared to HIV- subjects ($p < 0.05$). Although a higher quantity of PA was not associated with better HRV independent of age effects, participants across all groups with less sedentary behavior did exhibit higher RMSSD and SD1 compared to persons sitting more than 6 hours a day ($p < 0.05$).
Conclusions: HRV is an important biomarker of global health and predicts morbidity and mortality. Previous studies have observed that HIV is associated with impaired autonomic activity and lower HRV, but the effects of comorbid substance use have not been characterized and methods to improve HRV in this population have not been examined. Our findings indicate that HIV and METH use both reduce HRV, but these consequences may be ameliorated by decreasing time spent sitting or being inactive. Future interventions that focus on reducing the total quantity or interval duration of sedentary behavior may improve ANS function and health in persons with HIV and METH dependence.
Keywords: physical activity, heart rate variability, HIV, methamphetamine.
Disclosure: Nothing to Disclose.

W241. Functional Signaling of Thalamic Nucleus Reuniens Synaptic Inputs to CA1 Hippocampus in Awake, Behaving Mice

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Background: Anatomical and functional abnormalities have consistently been demonstrated in the prefrontal cortex (PFC) and hippocampus (HPC) of both patients and animals modeling various psychiatric disorders. Importantly, a single, ventral midline thalamic structure, the nucleus reuniens (NR) is considered to be a key link connecting the PFC back to the HPC. In fact, the NR is both densely and directly connected with the PFC, is the major source of excitatory thalamic inputs to the HPC through its selective projections to stratum lacunosum-moleculare (SLM) of CA1, and has recently been shown to be critical for intact cognitive functions, such as memory specificity and generalization, as well as for behavioral flexibility. The NR is thus well poised to contribute to the pathophysiology of symptoms in a variety of psychiatric disorders. Indeed, a theoretical model proposes that the NR may be directly involved in the pathogenesis of schizophrenia (SCZ) through interactions with the HPC (Lisman, 2010). However, as the NR has received surprisingly little attention to date, even the basic in vivo properties and function of NR inputs to CA1 (NR-CA1) relevant for behavior remain to be characterized, making it difficult to further directly test putative roles of this structure in models of psychiatric illness.
Methods: To assay activity dynamics of NR-CA1 inputs in awake mice (C57BL/6J; 6-10 weeks old), we developed an approach for 2-photon functional imaging of populations of individually identified NR synaptic boutons in CA1 of head-fixed mice during various behaviors. We used stereotaxic viral (rAAV Synapsin-GCaMP6f) injections targeted to NR to express the?fluorescent Ca2 + reporter GCaMP6f (whose signals serve as a surrogate for action potential activity) in NR axons projecting to CA1. To image Ca2 + dynamics in boutons in vivo, we implanted a headpost and chronic imaging window above CA1, and then head-fixed mice on a treadmill apparatus beneath a 2-photon microscope integrated with precise stimulus presentation and behavioral readout. We then extracted fluorescence signals from identified presynaptic NR boutons in SLM of CA1 during behavioral periods of the mouse resting/spontaneously running on the treadmill and responding to presentations (200 ms) of various sensory stimuli. We also developed a behavioral assay for memory specificity by adapting auditory trace fear conditioning (reported to require both PFC and HPC). In head-fixed, water-deprived mice ($> 80\%$ pre-deprivation weight), we used suppression of licking behavior to small water rewards as a measure of conditioned fear. In alternating trials (> 10 min. inter-trial interval), mice were presented with either a CS + tone that, after a 15 s trace period, was paired with an unconditioned stimulus (US; 200 ms air puffs to the snout x 5 at 1 Hz) or an unpaired CS- tone. 2 sessions for each conditioned stimulus tone were performed per day over several days.
Results: Ca2 + imaging in individual boutons revealed spontaneous activity in NR-CA1 inputs in mice even when stationary and at rest. However, during head-fixed running behavior in which postsynaptic CA1 cells are normally active, we found no significant changes in NR-CA1 inputs, indicating that treadmill running and NR-CA1 activity are uncoupled in head-fixed mice. As the external event driven activity of NR, and thus the types of information carried by NR-CA1 projections is unknown, we characterized baseline responses to discrete sensory stimuli of acoustic tones, light flashes, and air puffs to determine which modalities are

coded by NR inputs. We found very little responses to tone and light stimuli but significantly more robust fluorescence increases in NR-CA1 boutons with aversive air puff stimuli ($p < 0.01$, ANOVA). Using air puffs for the aversive US, we further developed a novel head-fixed auditory trace fear discrimination assay that can ultimately be integrated with simultaneous imaging of NR-CA1 activity. Over pairing sessions, US air puffs cause a suppression of licking to conditioned tone stimuli. We found that within 4-6 sessions, head-fixed mice show significantly greater lick suppression ($p < 0.05$, paired t-test) to a US-paired CS + tone compared to an unpaired CS- tone, indicating a sufficient degree of memory specificity during the learning assay.

Conclusions: Our results here begin to elucidate basic functional properties of the poorly understood NR-CA1 inputs in vivo and during waking behaviors. Our studies suggest that NR inputs are unlikely to play a role in driving the CA1 activity observed during head-fixed locomotion and that they selectively relay emotionally salient, aversive stimuli to the HPC compared to emotionally neutral sensory stimuli. Furthermore, we describe a behavioral assay during which NR-CA1 activity, along with activity of other CA1 circuit elements, could be selectively measured throughout the evolution of learning and memory acquisition over days to dissect out NR and CA1 mechanisms involved in systems level cognitive processes such as memory specificity and generalization. Finally, our studies lay the foundation for directly testing the putative role of NR inputs to CA1 in mediating pathophysiology and behavioral dysfunction in animal models of psychiatric illnesses such as schizophrenia.

Keywords: nucleus reuniens, hippocampus, in vivo, calcium imaging.

Disclosure: Mohsin Ahmed is a recipient of an American Psychiatric Foundation (APF) Schizophrenia Research Fellowship Award supported by Genentech, Inc.

W242. Abnormal Bioenergetics in Schizophrenia and Bipolar Disorders Studied by Dynamic 31P-MRS

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Background: Several lines of evidence suggest that patients with Schizophrenia (SZ) and Bipolar disorders (BP) exhibit mitochondrial and bioenergetic abnormalities. These include abnormal concentrations of metabolites involved in energy storage and use, observed using 1H- and 31P-magnetic resonance spectroscopy (MRS), dysfunctional oxidative phosphorylation, and altered mitochondria related gene expression, observed in postmortem studies. 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. Dynamic 31P-MRS approaches, 31P-magnetization transfer (31P-MT) and functional stimulation (31P-fMRS), were applied to accomplish these goals.

Methods: All study procedures were approved by the McLean Hospital Institutional Review Board and participants provided verbal and written informed consent. Four groups of participants with SZ and BP and corresponding age- and sex-matched healthy controls (HC) without any psychiatric or substance use disorders were recruited for these studies (31P-MT and 31P-fMRS for SZ and BP, respectively). SZ and BP patients were screened with a series of standard psychiatric diagnostic and research scales. 31P-MT and 31P-fMRS related acquisitions were separately conducted using a 4T whole-body scanner interfaced with a Varian INOVA console. Brain anatomic imaging and 31P-MRS were acquired using two separate, custom-designed dual-tuned surface coils for the frontal lobe and occipital lobe, respectively. For the 31P-MT experiment, the forward chemical exchange constant (kf) of the creatine kinase reaction (CK) was measured from the frontal lobe. 31P-fMRS from the visual cortex was performed on BP patients and healthy controls with 6 min rest-baseline and12 min visual stimulation (a 8 HZ flashing checkerboard), respectively.

Results: There was a substantial (22%) and statistically significant reductions in both CK kf and intracellular pH 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. For the visual stimulation on BP patients and HC, changes in metabolite levels during visual stimulation showed different patterns between the groups. During stimulation, HC had a statistically significant reduction in PCr but not in ATP. In contrast, BD patients had a statistically significant reduction in ATP but not in PCr. This may suggest a disease related failure to replenish ATP from PCr through CK enzyme catalysis during tissue activation.

Conclusions: Using novel 31P MRS approaches, we provide the first direct and compelling in vivo evidence for specific bioenergetic abnormalities in SZ and BP patients. The intracellular pH reduction suggests a shift from oxidative phosphorylation towards glycolysis. Additionally, reduced CK kf 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 of energy production at baseline is sufficient to approximate those seen in the HC. However, at times of high energy demand, ATP availability might be compromised because CK transfers high energy phosphates from storage in PCr to ATP to preserve relatively stable ATP levels. To test this hypothesis, we conducted 31P-fMRS with visual stimulation in BP patients and found that the energy substance levels exhibited a significantly altered pattern during visual stimulation. In contrast to the HC, BP patients experienced a reduction in ATP but not PCr. This again may suggest abnormality of CK enzyme activity. The current findings may provide a new biomarker of brain energy deficits in psychotic diseases.

Keywords: Bioenergetics, Psychosis, Mitochondria, Brain Stress.

Disclosure: Nothing to Disclose.

W243. Prefrontal Inputs to the Amygdala are Necessary for Safety Discrimination

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Background: A lack of discrimination between threat and safety, resulting in generalized fear is a cardinal symptom of Post-Traumatic-Stress Disorder and Generalized Anxiety Disorder. Activity in the prefrontal cortex (mPFC) has been repeatedly associated with decreased fear and anxiety in animals and in humans. Understanding how mPFC projections interact with downstream targets in squelching fear will allow us to harness those mechanisms to reduce fear and anxiety. One critical target of mPFC projections is the amygdala. Given the importance of the amygdala in processing fear, it is a central hub where the mPFC could act to inhibit fear-related behavior. The goal of the current work is to identify whether prefrontal inputs to the basolateral complex (BLA) of the amygdala have a causal role in discriminating safety from threat.
Methods: Optogenetics: To assess the impact of mPFC inputs on the BLA during behavior, bilateral injections of the light-activated inhibitory channel Archaerhodopsin (ArchT) into the mPFC were performed using adeno-associated-viral-vector (AAV2,5) under the control of the CaMKIIα promoter and conjugated to yellow-fluorescent-protein for placement verification (ArchT-YFP and YFP only as controls).. Electrophysiology: After waiting 6-8 weeks for viral expression at mPFC terminals in the BLA, mice were bilaterally implanted with optrodes (optical fibers coupled to tungsten stereotrodes) in the BLA and tungsten microelectrodes in the mPFC for simultaneous optogenetic silencing and neural data acquisition. Behavior: After a week to recover, mice were exposed to differential fear conditioning training for three days, where they learned to associate one frequency tone with a shock (0.4 mA, aversive conditioned stimulus, CS+) and another frequency tone with the absence of shock (CS-). On each training session, the 2 tones (2 and 8 kHz, counterbalanced for valence) were interleaved and presented 6 times each. Each tone presentation consisted of 50 ms pips, arriving at a rate of 1 Hz for 30 seconds. On day four, mice were presented with 20 tones in a pseudo-random order to test their recall of differential fear conditioning training. During fear recall, half of the tones (5 CS+ tones and 5 CS- tones) were presented in the presence of a green light (532 nm), shined bilaterally in the BLA, thereby inhibiting mPFC input. Cellular activity in the BLA and LFP in the mPFC were recorded throughout the fear recall test on Day 4 and the animals' behavior were monitored and recorded for offline analysis of freezing. Freezing was scored by an observer blind to CS valence (aversive or neutral) and animal group (ArchT-YFP versus YFP alone).
Results: Behavioral data analyses include a comparison of scored freezing to the CS+ and the CS- when mPFC inputs are active versus disrupted with light. Animals' discrimination of CS-types during recall ([% freezing to¬the CS+] – [% freezing to the CS-]) shows that at baseline (Light Off), animals froze more to the CS+ than the CS-. However, when mPFC inputs were inhibited, the same animals generalized fear across the two stimuli. Ongoing analyses are investigating the physiological effects of mPFC-BLA communication during the safe CS- when prefrontal inputs to the BLA are shut off.
Conclusions: My work has previously demonstrated that BLA neurons phase lock more to mPFC theta oscillations (4-12 Hz) when fear is relatively low, indicating that oscillations in the mPFC influence cellular firing in the BLA when fear is diminished. The current work demonstrates that mPFC inputs to the BLA have a causal role in safety discrimination.
Keywords: prefrontal, amygdala, fear generalization, optogenetics.
Disclosure: Nothing to Disclose.

W244. Loving-Kindness Meditation Practice Associated with Longer Telomeres in Women

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Background: Telomeres are nucleoprotein structures located at the ends of chromosomes which shorten with repetitive cell division and replication. Generally, telomeres shorten with age, but this shortening may be accelerated in the presence of cellular oxidative damage or chronic psychological stress. Shorter telomeres have been associated with earlier mortality (Cawthon et al., 2003). Therefore, telomere length may reflect the association of psychological well-being on health and longevity. A variety of health related factors have been associated with longer telomeres (non-smoking, healthy diet, exercise, being married; (Sun et al., 2012, Yen and Lung, 2012). In previous research, meditation practice was associated with higher telomerase activity (the enzyme that helps repair telomeres by adding DNA hexameric repeats to restore telomere length) in a group of individuals at the end of an intensive three-month full-time mediation retreat, compared to a control group (Jacobs et al., 2011). Loving-Kindness or metta meditation comes from the Vipassana Buddhist tradition, and focuses on developing a positive intention, unselfish kindness and warmth towards all people (Salzberg, 1995). Published work on Loving-Kindness Meditation (LKM) has demonstrated positive effects of this practice on the individual (more positive emotions, greater sense of purpose in life, and decreased illness symptoms such as headaches, congestion or weakness (Fredrickson et al., 2008). Because of this potential beneficial effect on psychological and physical health, we hypothesized that experienced LKM meditators would have longer telomeres than age, gender, and education-matched controls.
Methods: Individuals (>18 years old) with extensive training in LKM practice were recruited from meditation communities in New England. LKM participants had>4 years of regular, nearly daily LKM practice and overnight meditation retreat experience. Control participants (>18 years old) were required to not have experience with any meditation or yoga practices. Exclusion criteria for both groups included the current diagnosis of schizophrenia/psychosis, intellectual disability, substance abuse/depen-

dence, major depression, anxiety disorder, serious current medical illness, hormonal medication, inflammatory disease, diagnosis of cancer in the last 5 years, pregnancy or lactation. We recruited 75% of the LKM group first, and then recruited controls that resembled the LKM group, targeting the mean age (+/- 5 years), gender proportions, education level, and levels of depression history observed in the LKM group. Several LKM participants had a history of past major depressive episodes, and many had a graduate degree. Therefore, in order to prevent confounding, we over-enrolled control participants that had a past history of depression and a graduate level of education. Blood was obtained by venipuncture from an anticubital vein and collected into tubes containing Ficoll gel for separation of leukocytes by centrifugation. As described previously, the average relative leukocyte telomere length (LTL) is reported as the exponentiated sample ratio of telomere copy number to a 36B4 copy number (T/S) corrected for a reference sample (Cawthon, 2002). A Shapiro-Wilk test showed that our RTL data were not normally distributed ($W = 0.88$, $V = 4.38$, $z = 3.1$, $p = 0.00096$). A log transformation further failed to produce a normal distribution; therefore, we felt that the most conservative approach was to use non-parametric tests; we thus compared RTL between the two groups with a two-sample Wilcoxon rank-sum (Mann-Whitney) test.

Results: The meditation practitioners typically practiced LKM as part of a larger set of Vipassana meditation practices. The average number of lifetime hours of LKM was 512 hours, with a range of 125 to 1,825 hours. Overall meditation practice lifetime hours was 4,927, with a range of 432 to 20,695 hours. There were no significant differences in age, gender, race, education, or exposure to trauma. The control group did have a higher Body Mass Index (BMI); however, in the overall sample, being overweight ($BMI \geq 25$, $n = 16$ vs. $BMI < 25$, $n = 21$) was not associated with RTL ($z = -1.226$, $p = .22$). In addition, the LKM group had a higher rate of past depression. Overall, median relative telomere length (RTL) was longer in meditation practitioners (0.39) compared to controls (0.27), which was significant at the trend level (rank sum $z = -1.7$, $p = 0.083$). Among women participants, telomere length was significantly longer in meditators (0.42) compared to controls (0.31), ($z = -2.7$, $p = 0.007$). There was no significant difference between groups among male participants.

Conclusions: We found longer relative telomere lengths in individuals with years of experience in LKM, compared to age, gender, education, and trauma-matched individuals, and significantly longer RTL in women meditators than gender matched controls. Our finding suggests that LKM could have beneficial effects on mortality. These findings are in line with other research showing beneficial health effects of other-focused activities (spousal caregiving, community volunteering) and compassion or kindness towards others (altruism, forgiveness). For example, forgiveness of others has also be associated with greater longevity in a longitudinal study of elderly (Toussaint et al., 2012). Similarly, Pace et al found relationships between compassion meditation and lower markers of inflammation (Pace et al., 2009).

Keywords: telomeres, stress, meditation.

Disclosure: Nothing to Disclose.

W245. Longitudinal Trajectories of NREM Spindle Frequency Power Across Adolescence; Implications for Post-natal Brain Development

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Background: Strong evidence indicates that the human brain undergoes a major reorganization during late childhood and adolescence [1]. A sensitive indicator of post-natal brain maturation is the EEG of non-rapid eye movement (NREM) sleep. We have carried out a ten year longitudinal study of sleep EEG maturation, recording all-night sleep EEG twice-yearly in three cohorts: C6, beginning at age 6 yrs, C9 beginning at age 9 yrs and C12, beginning at age12 yrs (total $N = 93$). We previously described the maturational changes in NREM delta (1-4 Hz) and theta (4- Hz) [2]. We now present the longitudinal trajectory of sigma frequency power (SFP), the third distinctive set of NREM oscillations. SFP reflects the intensity of organized sleep spindle activity. Spindles are fusiform bursts of 12-15 Hz sinusoidal waves, 0.2-2 sec long, that occur in NREM but not in REM sleep. Spindles have been implicated in memory processes and neural integration and are driven by subcortical (thalamic, limbic) structures (c.f [3]).

Methods: Sleep EEG was recorded in subjects sleeping at home on their current school night schedules, confirmed by actigraphy. Standard methods of visual sleep stage scoring and FFT analysis were applied (for details, see [4]. Statistical evaluation was with mixed effect analysis which is particularly suited for longitudinal data.

Results: (1) Total sigma frequency power shows a biphasic trajectory across childhood-adolescence. After a small initial increase, the curve declines gradually until age 12, and then declines steeply between 12 and 16 years. (2) However, the curve for total sigma power is the resultant of different maturational curves for the lower and higher frequencies within that range: low and high frequencies within 12-15 Hz exhibit significantly different maturational trajectories: power in low sigma frequencies declines with age and power in high frequencies increases. (3) The frequency within 12-15 which produces the sigma peak in FFT spectra manifests a hugely significant linear increase across ages 6-18 yrs ($F1,852 = 123$, $p < 0.0001$). (4) Within the night, power in the low sigma frequencies increases significantly across NREM periods and power in the high sigma frequencies decreases significantly.

Conclusions: EEG power in the three major NREM frequency bands shows highly robust – and different – trajectories across childhood-adolescence. Although their overall trajectories differ, NREM delta, theta and low-frequency sigma power each show an accelerated decline across ages 12-16 yrs. We hypothesize that this is the age period of most rapid synaptic elimination. The accelerated synaptic elimination may underlie the emergence of adult "cognitive power", which appears to approach near-maximum levels at the end of the second decade of life (cf discussion in [1]). Taken together, the longitudinal data on sigma power maturation that we will present point to a general speeding up of central transmission; this could be another physiological manifestation of the streamlining of neural circuits produced by synaptic pruning. Supported by

R01MH62521 and R01HL116490. 1. Feinberg, I., Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? Journal of Psychiatric Research, 1982/1983. 17(4): p. 319-334. 2. Campbell, I.G. and I. Feinberg, Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain mat.

Keywords: Sleep, EEG, development, synaptic pruning.

Disclosure: Nothing to Disclose.

W246. Cortical and Hippocampal Microcircuits Involved in the Mechanism of Action of the New Antidepressant Drug Vortioxetine

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Background: Vortioxetine is a novel antidepressant approved for the treatment of major depressive disorder1,2. Vortioxetine shows a multimodal mode of action, being a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, and serotonin (5-HT) transporter (SERT) inhibitor2,3. Rodent radioligand occupancy data and human PET studies support a dose-dependent occupancy of all these targets corresponding to clinically doses of vortioxetine3,4. Vortioxetine increases the extracellular monoamine concentration in rat forebrain more than the selective serotonin reuptake inhibitors (SSRIs)2,3. 5-HT3 receptors, for which vortioxetine shows high affinity, appear to play a key role, given their selective expression on GABA interneurons and their control of inhibitory neurotransmission5. We previously reported that vortioxetine (but not escitalopram – ESC-) dose-dependently enhanced the discharge rate of pyramidal neurons in medial prefrontal cortex, an effect attributable to 5-HT3-R blockade6. In the present study we further examined the involvement of local 5-HT3-R-containing microcircuits in the mechanism of action of vortioxetine.

Methods: Electrophysiology. Single unit recordings of medial prefrontal cortex (mPFC) pyramidal neurons in anesthetized male Wistar rats. Microdialysis experiments were carried out in freely-moving rats implanted with dialysis probes in mPFC or ventral hippocampus (vHPC). Drugs were administered systemically or locally by reverse dialysis. Extracellular 5-HT was determined by HPLC with electrochemical detection.

Results: The administration of the 5-HT3-R agonist SR57227A (1.28 mg/kg i.v, injected before vortioxetine) did not alter the discharge rate of mPFC pyramidal neurons but fully prevented the enhancing effect of vortioxetine (0.2-1.6 mg/kg i.v.). In microdialysis experiments, ondansetron (5-HT3-R antagonist, 10 mg/kg s.c.) had no effect by itself on extracellular 5-HT in mPFC and vHPC but significantly augmented the enhancing effect of ESC (3.2 mg/kg s.c.) in both forebrain areas. Local ondansetron application (300 μM) by reverse dialysis in vHPC markedly augmented the extracellular 5-HT elevation produced by ESC (3.2 mg/kg s.c.). This suggests that 5-HT3-R blockade may reduce the inhibitory tone of local GABAergic elements controlling 5-HT release. Given the expression of GABAB receptors by 5-HT neurons, we examined whether the restoration of the GABAB tone by local baclofen application (GABAB agonist) could reverse the effect of 5-HT3-R blockade. Hence, co-perfusion of baclofen (100 μM) in vHPC cancelled the augmenting effect of ondansetron and returned extracellular 5-HT to the level attained with ESC alone. Likewise, local baclofen infusion (100 μM) markedly attenuated the effect of vortioxetine on extracellular 5-HT.

Conclusions: Together with previous observations, the present study indicates that 5-HT3-R blockade is involved in the elevation of pyramidal neuron discharge induced by vortioxetine. Moreover, 5-HT3-R blockade in GABA interneurons by vortioxetine appears to reduce local GABA tone on GABAB receptors controlling terminal 5-HT release, thereby increasing 5-HT release. These observations may account for the greater elevations of extracellular 5-HT produced by vortioxetine, as compared to SSRIs. References: [1] Alvarez, E., et al., 2012. Int J Neuropsychopharmacol 15; 589-600 [2] Sanchez, C, et al., 2014. Pharmacol Ther doi: 10.1016/j.pharmthera. 2014.07.001 [3] Mørk, A., et al., 2012. J Pharmacol Exp Ther 340; 666-675 [4] Pehrson AL, et al., 2013. Eur Neuropsychopharmacol 23; 33-145 [5] Puig, M.V., et al., 2004. Cereb Cortex 14; 1365-1375 [6] Riga, M.S., et al., 2013. Eur Neuropsychopharmacol 23(suppl 2); 393-394 Grants: Supported by Lundbeck A/S; PI12/00156 (ISCIII-Subdirección General de Evaluación y Fomento de la Investigación) and SAF2012-35183 (both cofinanced by the European Regional Development Fund).

Keywords: vortioxetine, 5-HT3 receptors, medial prefrontal cortex, ventral hippocampus.

Disclosure: Dr. Francesc Artigas is member of an Advisory Board for Lundbeck and has received research grants from Lundbeck.

W247. The Insular Cortex Bidirectionally Regulates the Reinstatement of Cocaine-seeking Behavior in Rats: Role of Corticotropin-releasing Factor Receptors

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Background: Although the medial prefrontal cortex (PFC) has long been implicated in the circuitry underlying cocaine-seeking behavior, less attention has been focused on the lateral PFC. However, evidence suggests that one part of the lateral PFC, the insular cortex (IC), is critically involved in craving and relapse for nicotine. Indeed, damage to the IC in humans produces a profound reduction in craving for nicotine and in nicotine use. Studies in rodents have revealed that inactivation of the posterior regions of the IC (PIc) reduces both nicotine self-administration and reinstatement for nicotine seeking, though little work has addressed the role of the IC in cocaine seeking. Prior work has found that the anterior regions of the IC, also known as the dorsal agranular IC (AId), are involved in cocaine seeking induced by contextual odors, whereas other work has found that lesions of the anterior IC, including the AId, potentiate cocaine seeking following self-administration and an abstinence period. Therefore, to

determine the role of the IC in the reinstatement of cocaine seeking, we investigated the roles of the AId and the PIc, using cue-induced and cocaine-prime.
Methods: Male Sprague-Dawley rats underwent surgeries for implantation of intravenous jugular catheters and bilateral cannulae, aimed at the AId or PIc. Rats then underwent cocaine self-administration, in which each active lever press produced an infusion of cocaine (200 μg per 50 μl infusion) as well as light and tone cues. After a minimum of two weeks of self-administration, rats underwent extinction training, in which active lever presses had no consequence. Rats then experienced a series of reinstatement tests: Cue-induced, cocaine-prime, and cues + cocaine-prime. Rats underwent each reinstatement twice in a counterbalanced manner. In the first experiment, rats received microinjections (0.2 μl) of the GABAB/A receptor agonists baclofen and muscimol (BM, 1 and 0.1 mM, respectively) into the AId immediately prior to the reinstatement sessions. In the second experiment, rats received BM microinjections into the PIc prior to the reinstatement sessions. Based on the results of the first experiment and prior studies suggesting a potential role for corticotropin-releasing factor (CRF) in the AId in craving and relapse, we conducted a third experiment, in which rats received intra-AId microinjections of the CRF1 antagonist antalarmin (6 mM) immediately prior to the reinstatement tests. For all reinstatement tests, active lever pressing was used as the index of reinstatement.
Results: AId inactivation, via BM microinjections, significantly reduced cue-induced reinstatement but significantly potentiated cocaine-prime reinstatement. Because the control group's levels of cocaine-prime reinstatement were relatively low, we also conducted a combination reinstatement (cues + cocaine-prime) and found that AId inactivation had no effect on such reinstatement. In addition, AId inactivation alone had no effect on a standard extinction session. PIc inactivation had no effect on any form of cocaine-seeking reinstatement, in contrast to the role of the PIc found with reinstatement of nicotine seeking. In the third experiment, blockade of CRF1 receptors produced identical effects to those found with AId inactivation: a reduction in cue-induced reinstatement, a potentiation of cocaine-prime reinstatement, and no effect on cues + cocaine-prime reinstatement. Therefore, the present findings indicate that the AId bidirectionally regulates the reinstatement of cocaine seeking, as AId inactivation and blockade of CRF1 receptors in the AId produced opposite effects on cue-induced vs. cocaine-prime reinstatement.
Conclusions: Prior work has suggested that the IC regulates craving and relapse due to its role in mediating interoceptive signals and that drugs of abuse produce a variety of interoceptive signals that serve as critical internal cues that drive craving and relapse. External cues, such as the light and tone cues used in the present study, have been hypothesized to trigger their own set of interoceptive cues that, in turn, produce relapse. The present results with cue-induced reinstatement are consistent with this hypothesis. However, the cocaine-prime reinstatement results suggest that the interoceptive cues produced by a cocaine injection have negative properties, consistent with previous studies suggesting that cocaine has both positive and negative properties and with previous work showing that the AId mediates aversive learning involved in conditioned place aversion. The present results also suggest that CRF1 receptors in the AId are involved in mediating these interoceptive cues. Together, the current findings suggest that the role of the IC in regulating drug-seeking behavior depends on the drug of abuse and on the nature of the reinstatement trigger.
Keywords: cocaine, drug prime, inactivation, self-administration.
Disclosure: Nothing to Disclose.

W248. PDE11A4, a Phosphodiesterase Enriched in the Ventral Hippocampus, is Required for Consolidation of Social Memories and Normal Social Approach Behaviors

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Background: Social deficits are key features of several neuropsychiatric disorders, such as autism, schizophrenia, and PTSD, yet no medicines are available to remedy these symptoms. Despite the fact that appropriate social behaviors are vital to thriving in one's environment, little is understood of the molecular mechanisms that control social behaviors or how social experiences modify these signaling pathways. Here, we show that Phosphodiesterase 11A (PDE11A), an enzyme that is restricted to the hippocampus and that breaks down cAMP and cGMP, may be a fundamental molecular mechanism of social behavior.
Methods: We conducted a number of experiments to determine if PDE11A4 regulates social behavior and if social experience feeds back to modulate PDE11A4. First, we tested male and female PDE11A knockout (KO) and sex-matched wild-type (WT) littermates for social vs non-social odor recognition (SOR vs nSOR) using odor-saturated wooden beads as stimuli. Next, we determined if PDE11A KO mice would form memories for non-social odors if they learned about them via social interactions instead of odor-saturated wooden beads. To test this, we used the social transmission of food preference (STFP) assay. We also tested PDE11A WT and KO mice in the 3-chamber social approach/social avoidance assay. Finally, we determined if social isolation affected trafficking of PDE11A4 by harvesting hippocampi from group-housed vs. single-housed C57BL/6J mice and conducted biochemical fractionation followed by Western Blot. All experimental protocols in animal studies were approved by the Institutional Animal Care and Use Committee at USC and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.
Results: Male and female PDE11A KO mice exhibited intact short-term memory (STM, 1 hour after training) for SOR but absolutely no long-term memory (LTM, 24 hours after training). This LTM deficit was reversed when PDE11A4 (the PDE11A isoform expressed in brain) was delivered back to the hippocampus of KO mice. Although PDE11A KO mice showed no LTM for SOR, they exhibited robust LTM for nSOR. Although PDE11A KO mice were able to form memories for non-social odors when presented on

wooden beads, they were not able to form memories of non-social odors when learned via a social interaction (i.e., STFP). Similar to results obtained in SOR, PDE11A KO mice demonstrated intact STM for STFP but no LTM. These results suggest that PDE11A4 is specifically required for the consolidation of social memories. In the social approach/social avoidance assay, when given the choice of exploring a cagemate versus a novel PDE11A WT mouse, neither male nor female PDE11A KO mice differed relative to WTs with regard to their approach behavior. When given the choice between a cagemate and a C57BL/6J, however, both male and female PDE11A KO mice approach the C57BL/6J mouse significantly less than do PDE11A WT mice. Since PDE11A appears to be required for intact social behaviors, we next asked if social experience might feed back to regulate PDE11A4. We found that 1 month of social isolation, vs. group housing, changed the compartmentalization of PDE11A4 protein within both the dorsal and ventral hippocampus. This isolation-induced shift in the compartmentalization of PDE11A4 was mimicked by a loss of phosphorylation at serines 117 and 124.
Conclusions: Together, our findings suggest that PDE11A4, a highly druggable target, regulates social behavior and is a key mechanism by which social experience modifies the brain. This suggests PDE11A4 may hold promise as a therapeutic target for disorders associated with social deficits, including schizophrenia, autism, and age-related disorders. With its highly restricted expression pattern, PDE11A4 is positioned to selectively restore aberrant cyclic nucleotide signaling in a brain region affected in numerous neuropsychiatric disorders without affecting signaling in other brain regions that might lead to unwanted side effects.
Keywords: PDE11, schizophrenia, autism, learning and memory.
Disclosure: Clinical Advisory Board Member, Asubio Pharmaceuticals, Inc.

W249. Generalization and Perception in Primate Networks: From Safety to Anxiety

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Background: I will focus on generalization of learning: how perception plays a role in the wider generalization following negative learning; what networks in the human brain contribute to the effect - both in healthy situations and in anxiety patients; and then describe single-cell network architecture in the primate amygdala that underlies the wide generalization.
Methods: We use human psychophysics, fMRI in healthy and in generalized-anxiety-disorder patients, and electrophysiology in behaving non-human-primates.
Results: We find that an interplay between the amygdala and the anterior-cingulate-cortex modulate activity in the amygdala and the primary-sensory-cortex (auditory), and this results in broad generalization and perceptual deterioration which is specific to patients. We also describe a single-cell network in the primate amygdala that underlie this broad generalization.
Conclusions: Our results suggest that these mechanisms can contribute to rationale behavior on one hand, but also to anxiety disorders if exaggerated, and that the amygdala and cingulate-cortex play a crucial role in modulating plasticity in sensory regions - in a specific manner to anxiety.
Keywords: fMRI, Amygdala, prefrontal cortex, electrophysiology.
Disclosure: Nothing to Disclose.

W250. A Network Informatics Approach to Identifying Points of Integration among Immune-related and Depression-related Pathways

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Background: Major Depressive Disorder (MDD) is a heterogeneous disease thought to be comprised of patient subpopulations that may have different molecular mechanisms as a key driver of the illness. Mounting evidence suggest that high levels of inflammation or perturbations to the immune system may be involved in the etiology of a subset of MDD patients. However little is understood about the mechanisms by which these processes might lead to a mood disorder. In this work, we take a bioinformatics approach aimed at identifying molecular points of crosstalk between genes known to be involved in the inflammation and immune regulation and those known or suspected to be involved in neural function, plasticity, and implicated in MDD.
Methods: The analysis was based on state-of-the-art network and pathway analytical techniques that help to identify targets shared by the immune system and depression. Gene lists were created for "Depression Genes" and "Immune Genes" through combination of manual curation, and mining of the MetaBase and Integrity databases. Network algorithms were run on these two gene sets with different strictness thresholds applied based on the number of manually curated PubMed articles that associate gene with MDD or immune disorders, respectively. Four network algorithms were applied to each gene list: Network Propagation (Vanunu et al., 2010), Random Walk (Kohler et al., 2008), Interconnectivity (Hsu et al., 2011) and Overconnectivitiy (Nikolsky et al., 2009). Algorithms were run separately on each gene list. We then sought genes that scored highly as key network nodes among both depression- and immune-gene lists, as likely points of cross-talk between the two systems.
Results: The top nodes discovered as likely points of intersection between gene lists are largely transcription factors. This is not surprising as transcription factors are key points of convergence, taking input from multiple signaling pathways and orchestrating the transcription of a collection of genes in response. The top 5 transcriptions factor implicated in an immunological role in depression are STAT3, CREB1, EGR1, SP1, IRF1. In addition, the top 10 ranked genes also included EP300, TNF, IL6, CTNNB, and CCL2.

Conclusions: Our results include a number of genes previously implicated in MDD, which were already members of our initial gene lists. Of those less well-studied, EP300, or KAT3B, is a paralogue of the CREB binding protein, is recruited by activated CREB, and acts as a histone acetyltransferase. It has been shown to play an essential role in long-term memory in transgenic animals models, and in humans mutations in the gene cause the mental retardation syndrome Rubinstein-Taybi. Inteferon Regulatory Factor 1 (IRF1) activator of interferons alpha and beta transcription, and has been proposed to play a role in the pathways linking P2RX7 to MDD. Searching for key network nodes at which the immune system and depression networks converge does not give rise to good candidates for drug development, as the impact of a perturbing these genes is expected to be disruptive. Rather they are a starting point from which a network can be constructed to identify candidate druggable targets that may ultimately modulate the activity of these downstream genes.
Keywords: informatics, network, major depression, immune.
Disclosure: Authors are employees of Janssen R&D, LLC or Thomson-Reuters. This work was funded by Janssen R&D, LLC.

W251. No Patient Left Behind: Neural Correlates of Reading Dysfunction and Sensory-based Remediation in Established and Prodromal Schizophrenia

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Background: Over recent years, deficits in basic sensory processing have become increasingly well established in schizophrenia (Sz) and tied to impairments in overall functional outcomes. Pathways by which these basic deficits lead to impairments in overall psychosocial function, however, remain to be determined. The present study integrates across convergent data sets investigating both the basis of reading impairments in Sz, and the effectiveness of sensory-based strategies in remediation both of reading ability and lower-level sensory functions.
Methods: Data will be presented from 3 convergent datasets. The first investigated reading performance in a cohort of 45 Sz patients (SzP), 19 clinical high risk (CHR) patients and 65 healthy comparison subjects (HC), along with sensory measures including mismatch negativity (MMN), tone matching and visual contrast sensitivity. The second evaluated reading in an additional cohort of 34 CHR vs. 33 HCs, along with tests of social and role function. A final dataset evaluate effects of sensory based reading remediation on both reading function and basic sensory function in a group of 11 SzP.
Results: SzP showed highly significant deficits in passage reading ability that remained significant even following covariation for general cognition. Deficits reflected a decline in performance relative to both premorbid ability and educational level completed. Deficits correlated highly with impaired sensory function as indexed by auditory MMN/tone matching and visual contrast sensitivity. Based on reading scores, up to 70% of SzP met criteria for an acquired dyslexia type pattern or reading impariment, with up to 50% reading below 8th great levels. CHRs showed isolated deficits in reading rate, with no impairment in phonological processing. In the expanded CHR cohort, deficits in reading fluency were again observed, along with correlations to both impaired MMN generation and social/role function. By contrast to reading fluency, reading comprehension remained intact. In the remediation study, pre-intervention deficits in reading ability correlated significantly with impaired activation of early visual regions, particularly those with sensitivity to low spatial frequency (LSF) stimulation. Active reading remediation led to significant improvements both in reading fluency and in fMRI activation of early visual regions. Changes in reading ability correlated significantly with increases in activation within early visual regions, suggesting significant bottom-up contributions.
Conclusions: In literate societies, minimum reading ability is required for social and occupational success. In Sz, a decline in basic sensory function during the late premorbid period leads to decline in reading and development of dyslexia-like impairments. In CHR, reading deficits are also significant and contribute to impaired social/occupational function. Reading deficits are not detected using standard single-word reading tests such as the WRAT which primarily reflect premorbid reading ability, but rather require dedicated tests of passage reading ability. Reading remediation in Sz leads to significant improvement in reading rate/accuracy along with improved basic sensory function, but may be limited by chronicity of the deficit. These findings call for more widespread screening of Sz and CHR cohorts for undetected dyslexia-like reading disability as a potential basis for persistent educational/occupational impairment, as well as for implementation of reading remediation programs at early stages of the illness. fMRI/ERP monitoring of sensory regions during may provide unique insights into neural bases of reading dysfunction in Sz.
Keywords: Schizophrenia, Cognition, Visual, Auditory.
Disclosure: Nothing to Disclose.

W252. CYP2A6 Genotype Differentially Shapes Striatal-Cortical Brain Circuits in Smokers vs. Nonsmokers

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Background: The hepatic enzyme cytochrome P450 (CYP2A6) is the main enzyme responsible for the metabolic inactivation of nicotine (Messina, et al., 1997). Genetic variation in CYP2A6 determine the rate of nicotine metabolism (Benowitz, et al., 2006) and are associated with smoking behaviors (Liu, et al., 2011; Styn, et al., 2013) and cessation success rates (Lerman, et al., 2010; Patterson, et al., 2008). Recently, a functional brain imaging study showed that genetic variation in CYP2A6 modulated neural reactivity to

smoking cues (Tang, et al., 2012). However, whether the CYP2A6 genotype directly shapes the intrinsic functional connectivity of brain networks/circuits and how such genotype effects, if any, interact with cigarette smoking remain unknown. The present study therefore was aimed to address these issues using resting-state fMRI and network analysis.
Methods: 48 smokers (Normal: Slow CYP2A6 genotype = 25:23) and 71 non-smokers (Normal: Slow CYP2A6 genotype = 28:43) participated in the study. All subjects underwent a resting-state fMRI scan for 6 min. Image preprocessing included slice-timing correction, head-motion correction, linear trend removal, and temporal band-pass filtering. Head motion, white matter and ventricle signals were regressed out from the fMRI signal. Functional connectivity strength, defined as the average functional connectivity between one voxel and all other voxels in the brain gray matter (Liang, et al., 2013), was computed for each subject. Genomic DNA was assayed from blood samples using standard protocols (Tang et al, 2012; Lerman et al., 2010). A 2 (Genotype: Normal, Slow) $\times$ 2 (Status: Smokers, Nonsmokers) ANCOVA was performed on the functional connectivity strength, including age, gender, IQ and years of education as covariance.
Results: Significant CYP2A6 GENOTYPE $\times$ SMOKING STATUS interactions were found in the dorsal anterior cingulate cortex (dACC), bilateral striatum, bilateral insula, dorsal lateral prefrontal cortex (DLPFC), and middle frontal gyrus ($p < 0.05$, corrected). Post-hoc analysis revealed that smokers with normal metabolizer genotype have higher functional connectivity strength than slow metabolizer genotype group in all regions; no CYP2A6 genotype effect was found in nonsmokers. To further explore specific brain circuits contributing to these GxE interactions, we used these regions as seeds in a functional connectivity analysis. Results revealed that a circuit between dACC and bilateral insula/PCC contributed the largest part to the dACC GxE effect. Circuit strength between the striatum and bilateral insula/dACC contributed primarily to the striatal GxE interaction. Main effects of CYP2A6 GENOTYPE were found in the middle cingulate cortex, dorsal media prefrontal cortex and bilateral insula ($p < 0.05$, corrected). The normal genotype group had higher functional connectivity strength than the slow genotype group in all regions regardless of smoking status. A main effect of SMOKING was found in the right middle temporal gyrus (MPG), with smokers showing decreased functional connectivity strength than nonsmokers across both genotypes.
Conclusions: This is the first study to reveal interactions of the CYP2A6 genotype and nicotine use on brain functional connectivity. The interactions were mainly located in structures within mesocorticolimbic circuits, including striatum, dACC and insula, which have been implicated in drug addiction (Koob and Volkow, 2010). Genetic variation in CYP2A6 had differential effects on brain circuits between smokers and nonsmokers. Smokers with slow CYP2A6 genotype showed lower functional connectivity strength than smokers with a normal CYP2A6 genotype, whereas no difference in functional connectivity strength was found in nonsmokers. Since the rate of nicotine metabolism is slower in individuals with the slow CYP2A6 genotype (Benowitz, et al., 2006), these result suggests that a greater amplitude and/or longer duration of nicotine in the brain may mediate the reduction in the functional connectivity strength in the mesocorticolimbic reward circuits. This is consistent with a previous study showing lower cue reactivity associated with the slow CYP2A6 genotype in smokers (Tang, et al., 2012) and suggests that that CYP2A6 genotype, likely through modifying the rate of nicotine.
Keywords: Gene X smoking status, Striatal cortical circuits, CYP2A6 genotype, Functional connectivity.
Disclosure: Nothing to Disclose.

W253. Dysregulated Neural Response to Unpredictable Social Evaluation in Adolescents with and At Risk for Social Anxiety Disorder

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Background: Social reticence (SR) in early childhood is the display of unoccupied, solitary behavior in the presence of familiar or unfamiliar peers. It is thought to result from a conflict between the motivation to engage in social interactions, and fear of receiving negative social evaluation. Stable SR during childhood may have an enduring influence on the capacity to establish successful peer relationships, and poses a risk for onset of social anxiety disorder (SAD) in adolescence. Interventions that target neural circuits dysregulated in adolescents at risk for, but yet to express SAD, may alleviate acute symptoms before they become chronic. Such interventions would facilitate normative social development and corresponding patterns of brain function, thereby preventing the high cost, and poor prognosis associated with adult SAD. Progress toward this goal has been hindered by limitations in neuroimaging paradigms, which bear little resemblance to contexts that elicit primary symptoms of adolescent SR or SAD. An fMRI paradigm that evokes fear of negative social evaluation, while modeling an ecologically valid social context, may address these limitations. 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 two fMRI studies to utilize the Virtual School paradigm. In these studies, we assess brain function as healthy adolescents with high or low SR, and those with or without SAD, anticipate social evaluation from predictable and unpredictable peers. When anticipating unpredictable social feedback from peers, we hypothesized that healthy adolescents with high vs. low, SR would differentially engage brain regions implicated in distress processing (dorsal anterior cingulate and anterior insula), while those with, vs. without, SAD would differentially engage brain regions implicated in fear processing (amygdala).
Methods: Study 1 participants were enrolled in a longitudinal study at 2-years of age, and re-assessed at 4, 5, and 7-years of age. Maternal reports and behavioral observations across assessments were used to generate a composite score of stable SR. At 11 years of age, a sub-sample of healthy adolescents ($M = 10.73$ years; $SD = .46$) with high ($N = 30$), and low childhood SR ($N = 24$) completed the present fMRI study. Study 2 includes preliminary data from

adolescents (M = 13.10 years; SD = 2.92) who were healthy (N = 15), or diagnosed with SAD (N = 7). In both studies, participants were told that they would play the "New Kid" at our Virtual School. They generated a cartoon avatar and personal profile they believed would be shown to a purported group of "Other Students." Participants learned the Other Students had a reputation for being 'nice,' 'unpredictable,' or 'mean.' Reputation comprehension was assessed prior to completing the Virtual School paradigm in the fMRI scanner. During the task, participants entered classrooms populated by the Other Students. For each trial, participants were cued to anticipate social evaluation when "Typing..." appeared above one of the Other Students. Because Other Students had an established reputation, participants anticipated different types of social evaluation from each peer. Unpredictable peers then provided 50% positive and negative feedback, while Nice and Mean peers provided 100% positive or 100% negative feedback (respectively). Participants then made a positive, negative, sarcastic, or avoidant responses to peer social evaluation.
Results: Both studies replicated prior behavioral findings (Jarcho et al., 2013), such that 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). Across both studies, brain activity varied by SR or expression of current SAD, during the anticipation of unpredictable, relative to predictable positive or negative social evaluation ($p < .005$, cluster extent > 20). Specifically, in Study 1, SR vs. non-SR adolescents exhibited heighted activity in dorsal anterior cingulate and insula, while in Study 2, SAD vs Healthy adolescents exhibited heightened activity in amygdala.
Conclusions: Adolescents at risk for SAD due to chronic childhood SR exhibit heightened engagement of brain regions implicated in the expression of distress while anticipating unpredictable vs. predictable social feedback. Preliminary data suggest that under the same conditions, adolescents with SAD exhibit a discrete pattern of responding, with heightened engagement of brain regions implicated in the expression of fear. These data suggest childhood SR may promote risk for SAD by eliciting distress processes while anticipating unpredictable social evaluation, which, over time, may lead to engagement of fear processes that precipitate the onset of SAD. Longitudinal studies are needed to more fully test this hypothesis.
Keywords: anxiety, social interactions, development, fMRI.
Disclosure: Nothing to Disclose.

W254. Rapid Antidepressant Ketamine Strengthens CRF-activated Amygdala Projections to Basilar Dendrites of Layer V Pyramidal Neurons in PL and AC but Not IL Subregions of Medial Prefrontal Cortex (mPFC)

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Background: A single sub-anesthetic dose of ketamine, a NMDA receptor blocker, produces a robust, prolonged antidepressant response in treatment-resistant depression. In chronic stress models ketamine reverses depression-like behaviors and associated deficits in apical spine density and serotonin (5-HT)- or hypocretin/orexin (hcrt)-activated EPSCs in layer V pyramidal cells of mPFC (Li et al., 2011). These apical deficits are rapidly reversed by ketamine through activation of the mTORC1 synaptogenic pathway (Li et al., 2010). Little is known, however, about the effects of ketamine on inputs to basilar dendrites of layer V cells. The basilar dendrites of layer V cells receive an excitatory input from glutaminergic pyramidal cells of the basolateral nucleus of the amygdala (BLA) (Gabbott et al., 2012). Pyramidal cells of the BLA express CRF-1 receptors (Van Pett et al., 2000) and are selectively depolarized by the stress-activated peptide corticotrophin releasing factor (CRF) (Giesbrecht et al., 2010). Preliminarily, CRF was found to generate excitatory postsynaptic potentials (EPSCs) in layer V pyramidal cells via CRF1 receptors in rat mPFC brain slices. Accordingly, we investigated: (1) whether CRF-induced EPSCs in mPFC depend upon BLA inputs to the basilar dendrites; (2) whether ketamine enhanced CRF activated EPSCs or increased dendritic spine density in the basilar field; (3) whether the CRF effects were reduced by chronic stress; and (4) whether ketamine effects differed between mPFC subregions.
Methods: Whole cell patch clamp recordings were from layer V pyramidal cells in PL, AC, and IL subregions of adult rat mPFC brain slices; EPSC responses to bath applied CRF (200 nM) and 5-HT were recorded. Cells were passively filled with Neurobiotin and later processed and imaged by 2-photon laser scanning for spine density analysis. Excitotoxin lesions were made in the BLA and recordings were performed after a lapse of two weeks to allow for degeneration of BLA-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 mTORC1 pathway. The effects of ketamine (10 mg/kg) were examined in brain slices 24 hrs following injection (i.p.) of the drug.
Results: We found: (1) that the effects of CRF in mPFC were largely dependent on the integrity of BLA inputs; (2) that ketamine pretreatment enhanced CRF-induced EPSCs with an associated increase in basilar dendritic spine density of layer V pyramidal cells of PL and AC but not IL subregions;; (3) that the effects of ketamine were mediated via the mTOR synaptogenic pathway as they were prevented by pretreatment with the mTORC1 blocker rapamycin; and (4) that chronic stress did not reduce CRF-induced EPSCs in basilar dendrites, contrasting with the marked loss of apically-targeted responses after chronic stress. (5) that ketamine increased apical EPSCs in all subregions including IL, which projects to the amygdaloid inhibitory intercalated neurons (ICN) that can suppress amygdaloid stress/fear responses (Quirk et al., 2003; Cho et al., 2013).
Conclusions: The main findings of this study are: (1) that the stress-activated hormone CRF induces EPSCs in basilar dendrites of mPFC layer V pyramidal cells via activation BLA inputs; (2) that ketamine pretreatment enhances CRF-induced EPSCs and increases basilar dendritic spine density in both PL and AC but not IL subregions; (3) that ketamine

does increase apical EPSCs in IL, which via its projection to ICN can suppress amygdaloid stress/fear responses; and (4) that CRF responses in the basilar domain are resistant to stress, contrasting with a marked reduction of responses to 5-HT and hcrt in the apical domain (Liu et al, 2008), conforming with the general rule that pyramidal cell basilar dendrites are resistant to chronic stress. The net result of these stress-induced changes is a shift in balance in favor CRF-activated basilar dendritic inputs over weakened apical inputs. These results are consistent with a disproportionate influence of the amygdala in chronic stress and major depression (see Price and Drevets, 2010). We propose that ketamine by restoring the strength of apical inputs to all subregions including IL would ameliorate this imbalance.

Keywords: antidepressant, stress, ketamine, CRF.
Disclosure: Nothing to Disclose.

W255. Endocannabinoid Hunger Signaling in the Gut is Controlled by Vagal Neurotransmission

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Background: The endocannabinoid system occupies an important position within the molecular and neural web that controls feeding, energy balance, and reward. Indeed, recent investigations from our laboratory reveal that tasting fat-rich foods initiates endocannabinoid signaling within the rodent proximal small intestine, which in turn, provides positive feedback to drive further fat intake. We now report results that suggest a broader role for 2-AG signaling in the control of hunger-induced feeding and the molecular and neural pathways that mediate these physiological processes.
Methods: Separate groups of male Sprague-Dawley rats were food deprived for 12-48 hours and intestinal levels of the endocannabinoid, 2-arachidonoyl-sn-glycerol (2-AG), and its precursor, 1-stearoyl-2-arachidonoyl-sn-glycerol (SAG), were quantified in the jejunum mucosa by liquid chromatography/mass spectrometry. The role for cholinergic neurotransmission in controlling 2-AG signaling in the gut was investigated in rats by quantifying 2-AG levels in the jejunum of free feeding and 24 h food deprived rats that received either (i) full subdiaphragmatic vagotomy, (ii) systemic administration of the general muscarinic acetylcholine (mAch) receptor antagonist, atropine (1mg per kg BW), or (iii) intraduodenal administration of the m3-subtype selective mAch receptor antagonist, DAU5884 (0.1 mg). Refeeding experiments were conducted to examine the ability for blocking cholinergic-mediated production of 2-AG or its actions at CB1Rs to inhibit refeeding in hungry rats (i.e., after 24 h food deprivation). All experimental protocols in animal studies were approved by the Institutional Animal Care and Use Committee at UCI and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.
Results: Food deprivation for longer than 12 hours, when compared to free-feeding animals, was met with increases in levels of 2-AG and its precursor, SAG, in the jejunum mucosa. Importantly, surgical disruption of vagal neurotransmission, or pharmacological inhibition of mAch receptors with atropine or local m3 mAch receptors normalized 2-AG levels in the jejunum mucosa, suggesting that 2-AG biosynthesis in the jejunum requires the activity of efferent vagal cholinergic signaling at mAchRs in the small intestine. We next asked whether hunger-induced 2-AG signaling at cannabinoid CB1Rs in the jejunum – initiated by the efferent vagus nerve – drives refeeding after 24 h of food deprivation. Pharmacological inhibition of CB1Rs receptors by systemic administration of the peripherally restricted CB1R antagonist, AM6545, reduced refeeding after 24 h of deprivation. Similarly, intraduodenal administration of the m3-subtype selective mAchR antagonist, DAU5884, at the same dose that normalized 2-AG levels after 24 h of food deprivation, reduced refeeding after a 24 h fast. Co-administration of AM6545 or DAU5884 resulted in no further inhibition of refeeding when compared to the effects on feeding for each drug individually.
Conclusions: Collectively, the evidence suggests that hunger drives the production of 2-AG in the jejunum through efferent vagal cholinergic neurotransmission at m3 mAch receptors in the proximal small intestine, which in turn, promotes refeeding through the 2-AG signaling at local CB1Rs. The specific subcellular localization of mAch receptors, the biosynthetic and degradative enzymes associated with the endocannabinoid system in the small intestine, and the downstream mediators by which activity at local CB1Rs signal to the brain to drive feeding remain to be determined and are currently under investigation.

Keywords: endocannabinoid, vagus, hunger, intestine.
Disclosure: Nothing to Disclose.

W256. Glucocorticoid-regulated Endocannabinoid Signaling in the Prelimbic Cortex Contributes to Stress-potentiated Cocaine Seeking

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Background: Recent studies suggest that, in many cases, rather than directly triggering cocaine use, stress may function as a "stage setter" such that stimuli that do not normally evoke relapse under stress-free conditions may precipitate use when exposure occurs in the context of stress. We have previously demonstrated that this stage-setting effect of stress is mediated by glucocorticoids. One site of action where glucocorticoids may regulate sensitivity to relapse triggers is the prelimbic cortex (PrL). Pyramidal cells in the PrL send excitatory projections to the nucleus accumbens core that have been suggested to be critical for drug-seeking behavior. The activity of these pyramidal cells is tightly regulated by GABAergic basket cells which in turn can be inhibited by endocannabinoids released from pyramidal cells in a retrograde manner through actions at CB1 receptors. In this study, we test the hypothesis that during periods of stress, glucocorticoids increase endocan-

nabinoid signaling via CB1 receptors in the PrL, thereby disinhibiting pyramidal cells and increasing relapse susceptibility.
Methods: Adult male Sprague Dawley rats were implanted with intravenous catheters and trained to self-administer cocaine (0.5 mg/kg/200 μl infusion) by pressing a lever under a fixed-ratio one schedule of reinforcement during daily 2-hr sessions. After 14 days of self-administration training, responding was extinguished by replacing the cocaine solution with saline during daily 2-hr sessions until extinction criteria were met (<10 active responses/session across 3 sessions), at which time reinstatement testing was conducted. The ability of stimuli (stress, corticosterone, etc…) to potentiate cocaine-induced reinstatement was examined by testing for reinstatement by these stimuli alone or in combination with a low, subthreshold cocaine dose (2.5 mg/kg, ip) that alone failed to evoke cocaine seeking. Initially rats were tested for the ability of a stressor -a 15-min period of intermittent electric footshock [0.5 mA, 0.5 s duration, mean inter-shock interval = 40 s (range 10-70 s)] delivered in the experimental chambers – to potentiate cocaine-induced reinstatement. Subsequently, the effects of various manipulations designed to reproduce or block the footshock-induced potentiation of reinstatement were examined.
Results: As previously reported, in rats with a history of daily 2 hr/day cocaine self-administration, footshock stress alone did not reinstate cocaine seeking, but rather potentiated reinstatement in response to a low cocaine dose (2.5 mg/kg, ip) that failed to reinstate cocaine seeking under control conditions (n = 7). Surgical adrenalectomy along with diurnal corticosterone replacement prevented this effect of footshock (n = 6), and the shock-induced potentiation was reproduced in non-stressed animals by administration of a physiologically relevant corticosterone dose (2.0 mg/kg, ip; 40 min pretreatment) that resulted in plasma levels (approximately 360 ng/ml) that were comparable to those measured after footshock (n = 6). The effects of stress on reinstatement likely involved corticosterone actions within the PrL, as bilateral intra-PrL delivery of corticosterone (0.05 μg/0.3 μl) also potentiated cocaine-induced reinstatement (n = 5) in a manner consistent with shock and stress-level corticosterone. Based on prior reports that corticosterone regulates endocannabinoid signaling in the PrL, we assessed the role of CB1 receptors in the stage-setting effects of stress on cocaine seeking. Shock-potentiated reinstatement was blocked by systemic administration of the CB1R antagonist, AM251 (1 or 3 mg/kg, ip; 30 min pretreatment; n = 5-6) at doses that failed to alter food-reinforced responding (FR4; 30-min sessions; 45 mg sucrose-sweetened pellets; n = 7-8) or locomotor activity (n = 5) and did not block reinstatement in response to a higher cocaine priming dose alone (10 mg/kg, ip; n = 7) in separate groups of rats. Moreover, the effects of shock or ip corticosterone on cocaine were prevented by bilateral administration of AM251 (300 ng/0.3 μl) into the PrL prior to reinstatement testing. In preliminary studies, we have examined the effects of shock alone, in drug-naïve rats, on endocannabinoid content in prefrontal cortical regions, including the PrL. Following 15 minutes of footshock, the endocannabinoids 2-arachidonylglycerol (2-AG) and anandamide (AEA) were extracted from dissected cortical regions (PrL, infralimbic, and anterior cingulate; n = 6-7 pool samples per region/group) and quantified by liquid chromatography-electrospray ionization-mass spectrometry. Shock increased AEA content in the PrL and 2-AG content in the anterior cingulate cortex.
Conclusions: Altogether, these findings pose corticosterone regulation of endocannabinoid signaling in the PrL as a potential mechanism through which stress and corticosterone can "set the stage" for use in recovering cocaine addicts, thereby heightening susceptibility to relapse. Supported by NIH/NIDA R01 DA015758 and R01 DA038663.
Keywords: stress, relapse, endocannabinoid, prelimbic.
Disclosure: Nothing to Disclose.

W257. Estrous-dependent Activation of the VTA During Extinction of Conditioned Fear

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Background: Women are twice as likely as men to develop Post Traumatic Stress Disorder (PTSD), but the neurobiological factors underlying this discrepancy are mostly unknown. In preclinical studies using fear conditioning and extinction paradigms, female rats with high estrogen levels during extinction learning exhibit facilitated extinction retrieval. The mechanisms underlying estrogen's beneficial effects are not known, but we have shown previously that a dopamine (DA) D1 receptor agonist can mimic the extinction-enhancing effects of estrogen, suggesting that estrogen-dopamine interactions may be important during extinction learning. Here we tested the hypothesis that dopaminergic activity during extinction of conditioned fear depends on the estrous cycle.
Methods: Gonadally intact female Long-Evans rats underwent a 2-day fear conditioning and extinction learning paradigm, and were sacrificed. We used immunohistochemistry for c-fos and tyrosine hydroxylase (TH) to quantify activation of DA neurons in the ventral tegmental area (VTA). We also evaluated c-fos expression in prelimbic (PL) and infralimbic (IL) regions of medial prefrontal cortex. Animals were grouped according to estrous phase during extinction.
Results: Despite equal numbers of total TH + cells in all groups, high-estradiol (proestrus) rats had a greater percentage of c-fos labeled TH + cells in the VTA than low-estradiol (estrus, metaestrus, diestrus) rats. c-fos expression in the IL and PL was also estrous-dependent.
Conclusions: Our findings suggest that the estrous cycle can influence the involvement of the VTA in extinction learning, which may underlie some of estrogen's effects on long-term maintenance of extinction.
Keywords: estrous, dopamine, fear extinction, ventral tegmental area.
Disclosure: Nothing to Disclose.

W258. Bimodal Role for Nucleus Accumbens Dynorphinergic Neurons in Aversion and Reward

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Background: The dynorphin/kappa opioid system is implicated in stress and vulnerability to drug abuse. It is thought that stress causes dynorphin release, activating kappa-opioid receptors (KOR) within both dopaminergic and serotonergic nuclei as well as their striatal targets. Dynorphinergic neurons within the striatum are particularly interesting for the study of stress and drug abuse, as prior studies have shown that KOR agonists inhibit dopamine and serotonin release in the nucleus accumbens (NAc), which regulates aversive behaviors. Consequently, much attention has focused on these systems in the modulation of KOR-mediated responses. Despite our current knowledge of central dynorphinergic cell body populations, a clear description of the axonal projections of these neurons is unknown. This information is crucial to further our understanding of the role of dynorphin in both aversion and reward behaviours.
Methods: We crossed the Cre-dependent tdTomato (Ai9) reporter mouse to a mouse expressing Cre recombinase under the same promoter as dynorphin (Dyn-Cre) so only dynorphinergic cells express tdTomato. This allows complete visualization of dynorphinergic circuitry throughout the brain. We also virally targeted channelrhodopsin-2 to striatal dynorphinergic neurons and optogenetically activated neuronal populations in both the dorsal and ventral NAc shell to measure aversion and reward behaviors using place preference, aversion, and operant conditioning. We also designed an opto-dialysis probe that we implanted in the NAc of mice injected with channelrhodopsin-2, which allowed collection of dialysate before, during and after stimulation to detect dynorphin. Samples were analysed using liquid chromatography-mass spectrometry (LC-MS) detection.
Results: Using dynorphin-cre-tDtomato cross we found robust dynorphin expression in cell bodies throughout the brainstem and forebrain. Clear visualization of intact projections throughout the brain and dynorphinergic projections can be seen from and within the cortex, striatum, amygdala, and numerous monoaminergic nuclei. We investigated whether specific modulation of dynorphinergic neuronal firing in the NAc is sufficient to induce aversive behaviors. This activation significantly increased c-Fos immunoreactivity in dynorphinergic neurons. Furthermore, activation of ventral NAc shell induced conditioned and real-time aversive behavior, while dorsal NAc shell stimulation resulted in a place preference, which was also shown to be positively reinforcing in an operant task paradigm. We were also able to detect an increase in dynorphin release following stimulation of dynorphin containing cell bodies in the ventral NAc.
Conclusions: The results presented here for the first time show a discrete subregion of dynorphin-containing cells in the ventral shell of the accumbens that mediate aversion through dynorphin release and KOR activation. Furthermore, dorsal accumbens dynorphin cell activity is consistent with reward, perhaps via a classical dopamine D1 pathway, but this hypothesis will require further study. For the first time we are able to detect the release of dynorphin following photostimulation of dynorphin containing cells. Understanding the mechanisms by which the dynorphin/kappa opioid system regulates negative affective behaviors will provide valuable insight into potential treatments for stress disorders and drug abuse.
Keywords: dynorphin, nucleus accumbens, reward, aversion.
Disclosure: Nothing to Disclose.

W259. Impaired Functional Connectivity Within and Between Frontostriatal Circuits is Associated with Impulsivity and Compulsivity in Cocaine Users

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Background: The striatum, through fronto-striato-thalamo loops, is known to be involved in the development and maintenance of cocaine dependence, from ventral striatal (VS) support of initial cocaine use to dorsal striatal (DS) support of habitual use. Resting state functional connectivity (rsFC) has been used to elucidate specific brain regions whose activity correlates with various striatal subregions and to relate these circuits to symptom severity in obsessive compulsive disorder, which has core features in common with cocaine dependence, compulsive use of cocaine being a defining feature of dependence. Impulsivity both predisposes to cocaine dependence and is worsened by cocaine use. In this study, we used rsFC from six striatal seeds to uncover regions whose connectivity to striatum distinguishes chronic cocaine users (CU) from healthy controls (HC). We then investigated these results for relations with compulsivity of cocaine use and other disease-related features (impulsivity and drug use patterns).
Methods: 56 non-treatment seeking CU and 56 HC were matched on age, gender, years of formal education, race, WAIS vocabulary score, and smoking status. All subjects underwent a standard 6-minute, eyes closed, resting EPI scan. Bilateral 4-mm-radius spherical seeds were placed in 6 striatal regions: ventral striatum inferior and superior parts (VSi and VSs, respectively), dorsal caudate (DC), ventral rostral putamen (VRP), dorsal rostral putamen (DRP), and dorsal caudal putamen (DCP). For each region, a 2x2 (hemisphere x group) ANOVA was carried out in a mask of brain areas with significant rsFC to at least one of the bilateral seeds in either group, covarying for age and head motion. Average rsFC from ROIs showing group differences were regressed against current cocaine use ($/week), years of cocaine use, and BIS-11 (total score and 3 subscale scores). Two circuits previously shown to be related to severity of OCD and nicotine dependence and related to putative 'Go' and 'Stop' circuits, respectively, differed between groups (see Results). These were subtracted and regressed against number of compulsivity-related DSM-IV

cocaine dependence criteria met by CU participants in an effort to identify a metric that might characterize cocaine dependence, recognizing its phenotypic similarity to both OCD and nicotine dependence.
Results: CU had 12.64 ± 6.40 years of cocaine use, currently used $246.70 ± 168.94 per week, met 4.5 ± 1.6 DSM-IV dependence criteria and 3.5 ± 1.3 out of the 5 criteria related to compulsive use. CU showed higher BIS-11 impulsivity than HC. Both groups showed similar patterns of rsFC with each striatal seed, consistent with networks previously reported. ANOVA results revealed lower rsFC in CU broadly in striatal-cingulate, -insula, -hippocampal/amygdala and –striatum circuits and higher rsFC in CU in striatal-frontal circuits, specifically DC-dorsolateral prefrontal cortex (DLPFC) and VS-inferior prefrontal (iPFC)/lateral orbitofrontal cortex (lOFC). rDC-bilateral DLPFC rsFC correlated with current cocaine use and with BIS-11 total score. rDC-rDLPFC was positively correlated with the Attention ($r = 0.473$, $p = 0.026$) and Non-planning BIS subscores ($r = 0.516$, $p = 0.014$), while the rDC-lDLPFC was positively correlated with the Motor BIS subscores ($r = 0.595$, $p = 0.003$) in CU only. No relationships with years of cocaine use were found. VS-iPFC/lOFC is known to be associated with severity of symptoms in OCD and VS-dACC with severity of nicotine dependence. Both of these circuits showed significant group or group x hemisphere results in the main ANOVA. The difference in rsFC between these two circuits (Bonferroni corrected for the 4 possible combinations present in the main ANOVA results) was significantly correlated with number of DSM-IV compulsivity-related symptoms ($r = 0.393$, $p = 0.003$).
Conclusions: We document region specific increases and decreases in striatal rsFC to various brain regions in CU relative to controls. Building on previous work in OCD and nicotine dependence, we derived a metric based on the balance of rsFC in striatal circuits that correlates with compulsivity symptoms in CU, which may prove to be a useful biomarker of cocaine dependence. Further, we demonstrate a relationship between DC-DLPFC rsFC and impulsivity that is present only in CU. DLPFC is thought to be an important region for executive control, and demonstrates increased activity in CU to cocaine cues and cocaine administration. Stimulation of DPLPFC using rTMS has been proposed as an addiction treatment. However, rTMS stimulation of DLPFC increases the attentional blink to alcohol cues in alcohol dependent individuals. Finding a positive relationship between DC-DLPFC rsFC and impulsivity only in CU may indicate that the circuit is functioning in an aberrant manner that supports impulsivity rather than executive control in CU and urges caution in stimulating DLPFC for therapeutic goals in addiction. Finding the relationship only in CU may indicate that this circuit is related to the worsening of impulsivity seen after cocaine exposure. Alternatively, it could relate to pre-existing impulsivity shared with non-using siblings but with differing neural underpinnings from impulsivity seen in HC. Striatal rsFC shows promise for developing brain based biomarkers of cocaine dependence and related features that may prove useful in developing new treatment targets.
Keywords: cocaine, striatum, connectivity, biomarkers.
Disclosure: Nothing to Disclose.

W260. Correlation Between Gene Expression Profiles in Peripheral Blood Mononuclear Cells and Structural and Functional Brain Networks in Chronic Visceral Pain

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Background: Bidirectional interactions between the brain and the immune system have been implicated in the pathophysiology of stress sensitive psychiatric and chronic pain disorders (Irwin and Cole, 2011). Distinct gene expression profiles in peripheral blood mononuclear cells (PBMCs) consistent with increased activity of the sympathetic nervous system (SNS) have been described in preclinical and clinical populations under stress ("conserved transcriptional response to adversity" (CTRA) (Powell et al., 2013). These profiles are characterized by increased expression of pro-inflammatory genes and decreased expression of genes involved in innate antiviral responses and IgG antibody production. On the other hand, migration of primed PBMCs including monocytes to the brain, have resulted in regional glia activation and neuroinflammation (Wohleb et al., 2011, 2013). Structural and functional changes in several brain networks have been identified in chronic pain disorders, including the salience, sensorimotor and central autonomic networks (Gupta et al., 2013). AIMS: To use different analytic approaches in order to test the following two complementary hypotheses: 1) IBS subjects show altered gene expression profiles in PBMCs, consistent with the CTRA pattern, which are correlated with structural changes in brain regions of the salience and emotional arousal networks. 2) Inflammatory gene expression profiles are correlated with functional changes in the salience network.
Methods: The sample consisted of 40 individuals (20 IBS; 20 healthy controls [HCs]) completed structural and resting state MRI scans. Gene expression was assessed using human transcriptome array 2 (HTA-2, Affymetrix). Data were normalized using robust multi array (rma) algorithm extracted from the CEL files using Expression console (Affymetrix). The following analyses were conducted to test two main hypotheses: 1. Determination of signal transduction pathway activity in PBMCs using bioinformatic analyses and the correlation of these activity profiles in morphological brain measures. 2. Differential expression of PBMC functional gene clustering using a fold change of 1.2 using DAVID bioinformatics and influence of the inflammatory gene profiles ($N = 12$) on resting state salience network activity.
Results: No significant group differences in the activity of key pro-inflammatory transcription or expression factors were detected. 1: Transcript origin analyses indicated that IBS up-regulated genes in immature (CD16-) monocytes showing classical proimflammatory M1 activation profiles and alternately activated M2 gene expression profiles. Differential signaling by the myeloid lineage transcription factor MZF-1 was positively associated with the morphology of brain regions involving the salience and emotional

arousal networks, including bilateral amygdala, hippocampal, and anterior insula volume and cortical thickness. 2. Group differences in the modulation of PBMC gene expression levels on the salience network connectivity were observed. In HCs compared to IBS, proinflammatory genes (IL6, APOL2) were positively correlated with mid cingulate and superior temporal gyrus connectivity within salience network, whereas anti-inflammatory genes (KRT8, APOA4) were negatively correlated with the insula, putamen, and supramarginal gyrus connectivity within the salience network.

Conclusions: Together these results suggest: 1. The up-regulation of genes in IBS patients suggest a pattern of increased myeloid lineage cell development in the immune system, and may stem from tonically increased SNS signaling to bone marrow myelopoietic processes. 2. There appears to be a top-down role in that key morphological changes of regions within the salience and emotional arousal networks are correlated with differences in myelopoetic processes and gene expression in the peripheral immune system. 3. There also appears to be a group difference in the bottom-up modulatory role of the PBMC inflammatory gene expression levels on salience network connectivity. This suggests that PBMC abnormalities may be associated with the priming of monocytes migrating to the brain and consequently induction of regional neuroinflammatory changes affecting network connectivity. Such bottom up signaling may play a role in the development of visceral hypersensitivity, and increased anxiety during periods of stress.

Keywords: peripheral blood mononuclear cells, immune system, salience network, morphological and resting state brain activity.

Disclosure: Supported by NIH grants P30 DK041301, R01 DK048351, P50DK64539. UCLA Ahmanson-Lovelace Brain Mapping Center (Pilot Scanning).

W261. Lesions of the Orbitofrontal Cortex Reduce Risk-taking in Rats

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Background: Maladaptive risk-taking is characteristic of several psychiatric conditions, including addiction, schizophrenia, and anorexia nervosa. It is therefore important to understand the neurobiology underlying normal risk-taking to determine how this behavior becomes compromised in a diseased state. One brain region that has been heavily implicated in decision-making is the orbitofrontal cortex (OFC). However, its specific involvement in decision-making under conditions of risk of explicit punishment is unknown.

Methods: We used a rodent model of risk-taking behavior [the Risky Decision-Making Task (RDT)] in which rats chose between a small, "safe" reward (1 food pellet), and a large reward (3 food pellets) that was accompanied by varying probabilities of mild footshock punishment. Rats ($n = 16$) were trained in the RDT until stable performance emerged, after which they received either neurotoxic lesions of the OFC or sham surgery. Rats were then re-tested in the RDT. After stable performance was attained, rats were tested in a reward discrimination task, in which they chose between the small and large rewards in the absence of punishment. To determine whether lesions altered motivation to obtain food, rats were then tested on various fixed ratio schedules of reinforcement (lever pressing for food under FR1, FR3, FR10, FR20, and FR40 schedules; 1 schedule/day). Finally, rats were tested in the elevated plus maze (EPM), a common behavioral assay of anxiety. After completion of the experiment, rats were euthanized and brain tissue was analyzed for lesion verification.

Results: Prior to surgery, there were no differences in performance in the RDT between lesioned and sham groups. After surgery, however, lesioned animals significantly decreased their choice of the large, risky reward relative to both pre-surgery performance and sham controls. This decrease in risk-taking could not be accounted for by an impaired ability to discriminate between the small and large rewards, as both sham and lesioned rats showed equivalent preference for the large reward on the reward magnitude discrimination task. There were also no differences in lever pressing between the groups across all FR schedules. Finally, there were no group differences on any of the EPM measures, suggesting that the lesion-induced risk aversion was not due to increased anxiety.

Conclusions: These results demonstrate a role for the OFC in guiding choice behavior in situations that involve potentially negative and harmful consequences. Given its role in tracking the value of expected outcomes, the OFC may be important for monitoring and updating the values of the small and large rewards as the risk of punishment changes over the course of the task. Future experiments will focus on delineating the specific types of information encoded by the OFC during risky decision-making.

Keywords: orbitofrontal cortex, risk, decision-making.

Disclosure: Nothing to Disclose.

W262. How Do Critical Nodes in the Striatum Impact on Downstream Basal Ganglia Circuitry?

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Background: Although traditionally, the cortico-basal ganglia circuit has been characterized as having segregated, parallel pathways (e.g., Alexander & Crutcher, 1990), we now know that these pathways consistently overlap, and are not segregated (Haber et al., 2006; Averbeck et al., 2014; Calzavara et al., 2007). The striatum, in particular, receives converging connections from functionally distinct prefrontal cortical (PFC) regions. For example, dense projections from the ventromedial PFC (vmPFC) and dorsal anterior cingulate cortex (dACC) do not occupy completely separate territories within the striatum, but overlap. These areas of convergence ("nodes") are critical to our understanding of basal ganglia function. They provide an anatomical substrate for integration among different networks, and may represent important sites for plasticity and adaptation in psychiatric disorders. In this project, our aim is to follow

these converging connections from PFC through downstream basal ganglia regions, beginning with the striato-pallidal projection. Prior work has shown that striatal axons maintain a general topography in the pallidum. However, these studies did not distinguish among specific areas within the striatum based on their PFC inputs, so it is unclear whether information from functionally diverse PFC regions converges further in the pallidum. If it does, the pallidum may play an integrating role similar to that of the striatum; if it does not, the function of the pallidum may be different. Thus, our first goal was to demonstrate the organization of the striato-pallidal connections according to those areas of the striatum receiving projections from different combinations of vmPFC, dACC, dorsolateral PFC (dlPFC), dorsomedial PFC (dmPFC), ventrolateral PFC (vlPFC), and orbitofrontal cortex (OFC). Our second goal was to determine whether striatal nodes (zones of overlap) project particularly broadly within the pallidum.
Methods: To map striatal projections to the pallidum, we placed 54 anterograde/bidirectional tracers in specific regions of the macaque striatum, according to their combinations of frontal cortical inputs. Thus, some striatal injections were in areas receiving dlPFC and dACC inputs; others were in areas receiving inputs vmPFC and dACC inputs; others received vmPFC, dlPFC, dACC, and OFC inputs, and so on (defined in Averbeck et al., 2014). 20 cases were chosen (based on quality of transport and lack of contamination) to be analyzed in detail and combined into a 3-D model. We used Neurolucida software to outline dense terminal fields in the external (GPe) and internal (GPi) segments of the globus pallidus, and ventral pallidum (VP). We then used the 3-D rendering program IMOD to transfer these terminal fields to a standard macaque brain for comparison and visualization purposes.
Results: Our preliminary results indicate that functional striatal regions project mainly to unique zones of the pallidum, with relatively little overlap. For example, an injection into the ventral striatal region receiving vmPFC projections results in anterograde labeling mainly in the medial VP, whereas an injection into the striatal region receiving a combination of dACC and OFC projections labels a more lateral portion of the VP. Striatal areas receiving both dlPFC and dACC projections terminate in a different location, mainly in the dorsal pallidum. There is little or no overlap among these terminal fields. Moreover, those injections placed in striatal nodes with strongly converging frontal inputs do not appear to result in broader pallidal projections.
Conclusions: The striatum is a known site of cortical integration. However, the literature has been divided on whether cortical information passing through the striatum is further integrated in the pallidum (Hedreen & DeLong 1991; Hazrati & Parent, 1992). Although additional analyses are needed, our results indicate that terminals from striatal nodes do not overlap in the pallidum. The pallidum may integrate inputs via a different mechanism, such as highly arborized dendrites. However, our results raise the possibility that the pallidum may not be a site of further cortical integration. Instead, pallidal neurons may perform "dimensionality reduction" on the complex information found in the striatum (Bergman et al., 1998). Our map can also guide neuroimaging studies of psychiatric disorders. To understand the disruptions underlying PFC-basal ganglia abnormalities, it is essential to examine specific subregions within each component of the circuit, including the pallidum. Finally, the GPi is a surgical target for Parkinson's Disease and Tourette Syndrome. Our 3-D rendering of striato-pallidal terminals highlights the specific connections affected by such interventions.
Keywords: Basal Ganglia, Prefrontal Cortex, Striatum, Globus Pallidus.
Disclosure: Nothing to Disclose.

W263. Glutamate Signaling Dynamics in the Rat Nucleus Accumbens Core and Prelimbic Cortex During Pavlovian Conditioned Approach

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Background: There is evidence that drug-seeking behavior induced by drug-associated cues transcend their ability to predict drug reinforcement. Studies in preclinical models using Pavlovian conditioned approach (PCA) have shown that individual differences in 'incentive salience' of a food-associated stimulus (sign-tracking vs. goal-tracking behavior) are predictive of abuse-like behavior. Considering the importance of glutamate dynamics in the nucleus accumbens and the prelimbic cortex in drug abuse, this research sought to explore glutamate signaling in freely-moving rats during PCA.
Methods: Rats were trained to discriminate a food-predictive lever conditioned stimulus from one that was not paired with food. We then used microelectrode arrays selective for glutamate to measure phasic glutamate release within the nucleus accumbens or prelimbic cortex during PCA performance.
Results: Our results demonstrate differential phasic glutamate signaling between the nucleus accumbens core and the prelimbic cortex during sign-tracking behavior to a reward-predictive stimulus within PCA performance. Specifically, phasic glutamate signals in the nucleus accumbens core were slower (20-30s), bimodal-shaped peaks of approximately 2-4 μM in amplitude, with one mode of the peak elicited by presentation of the reward-associated stimulus (lever) and the other elicited by the reward (food pellet). Phasic glutamate signals within the prelimbic cortex were faster (8-12s), leptokurtic-like peaks with amplitudes of approximately 7-12 μM, elicited only by food. Additionally, no glutamate release was associated with the stimulus not paired with food in either the nucleus accumbens or the prelimbic cortex.
Conclusions: These data indicate a clear role for region-specific phasic glutamate signaling within the mesocorticolimbic pathway in stimulus-reward learning and incentive salience attribution. The data provide insight into the differential glutamatergic signaling dynamics in brain regions associated with abuse-like behavior that may further understanding of the behavioral and neurochemical mechanisms that underlie abuse-related behavior.
Keywords: incentive salience, glutamate, addiction, sign-tracking.
Disclosure: Nothing to Disclose.

W264. Downstream from Dopamine: DREADD-based Stimulation of VTA Dopamine Efferents to mPFC or NAc During Cocaine Seeking

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Background: Ventral Tegmental Area (VTA) is crucial for many reward-related behaviors, and both dopamine (DA) and non-DA neurons there play complex roles in reward and motivation. In addition, dopamine neurons themselves are heterogeneous, and distinct functions have been proposed for DA neurons projecting to medial prefrontal cortex (mPFC) and nucleus accumbens (NAc). 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 otherwise pharmacologically inert). DREADD-expressing neurons can therefore be experimentally controlled in a highly selective, "lock-and-key" manner. DREADDs can be targeted to VTA DA neurons via local microinjections of viral vectors containing a floxed DREADD gene into transgenic rats, whose dopamine neurons express Cre recombinase (TH::Cre rats). DA neurons also traffic DREADDs to axonal processes, including those in NAc and mPFC, and local microinjection of CNO into these structures can cause specific activation or inactivation of their VTA DAergic afferents.
Methods: Here, we used viral vectors to express excitatory, Gq-coupled DREADDs in VTA dopamine neurons in TH::Cre transgenic rats. We trained rats to self-administer cocaine + a tone/light cue, then extinguished this behavior over 7 + days. On test days, we microinjected CNO into either mPFC or NAc of rats in the absence or presence of drug-associated cues to determine effects of cocaine seeking.
Results: We examined the effects of local microinjections of CNO (1mM/0.3ul) into either mPFC or NAc on cocaine seeking. In the same animals, we examined whether 1) stimulating VTA DA projections to mPFC or NAc would induce reinstatement of cocaine seeking after extinction, and 2) similar stimulation would increase the degree of cue-induced cocaine seeking. Distinct patterns of effects on cocaine seeking were observed after stimulation of VTA DA neuron projections to mPFC and NAc.
Conclusions: Our results demonstrate the utility of DREADDs to excite particular anatomical projections of phenotypically defined neurons, such as mPFC- or NAc-projecting VTA DA neurons. We directly compared the roles played by these subpopulations of VTA DA neurons projecting to mPFC or NAc in reinstatement of cocaine seeking behavior, and found distinct patterns of effects. These results will advance our knowledge of VTA DA neuron functional heterogeneity, and further demonstrate the usefulness of DREADDs as a behavioral neuroscience tool, and as a potential future intervention for psychiatric disorders like addiction. Supported by PHS grants R37-DA006214, F32-DA026692, K99-DA035251.
Keywords: dopamine, prefrontal cortex, nucleus accumbens, relapse.
Disclosure: Nothing to Disclose.

W265. GIRK3 Subunit in Midbrain Neurons Controls Ethanol Binge Drinking

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Background: G protein-gated inwardly-rectifying potassium (GIRK) channels are critical regulators of neuronal excitability and can be directly activated by ethanol. Intriguingly, constitutive deletion of the GIRK3 subunit has minimal phenotypic consequences except in response to drugs of abuse. Here, we investigated how the GIRK3 subunit contributes to the behavioral effects of ethanol.
Methods: GIRK3 knockout (KO) mice and their wildtype counterparts were subjected to tests of ethanol-induced ataxia, sedation, hypothermia and withdrawal hyperexcitability, as well as to various paradigms of voluntary ethanol consumption. A lentiviral vector was used to examine the role of GIRK3 expression in the ventral tegmental area (VTA). In addition, recordings from putative dopaminergic (DA) neurons were obtained in the VTA and microdialysis was used to measure extracellular levels of DA in the nucleus accumbens.
Results: We found that constitutive deletion of GIRK3 selectively increased ethanol binge-like drinking, without affecting sensitivity to ethanol intoxication or continuous-access drinking. Virally-mediated expression of GIRK3 in the VTA reversed the phenotype of GIRK3 KO mice and further decreased the intake of their wild-type counterparts. In addition, GIRK3 KO mice showed a blunted response of the mesolimbic DA pathway to ethanol, as assessed by ethanol-induced excitation of VTA DA neurons and DA release in the nucleus accumbens.
Conclusions: These findings support the notion that the subunit composition of VTA GIRK channels is a critical determinant of DA neurons sensitivity to drugs of abuse. Furthermore, our study reveals the behavioral impact of this cellular effect, whereby the level of GIRK3 expression in the VTA tunes ethanol intake under binge-type conditions: the more GIRK3, the less ethanol drinking.
Keywords: Kir3, Kcnj9, alcohol, reward.
Disclosure: Nothing to Disclose.

W266. Cortico-Striatal Circuitry Underlying Cognitive Control over Attentional Bias in Addiction

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Background: The striatum is critical for the formation and maintenance of drug habits in addiction. Drug habits are associated with a strong attentional bias for the drug of abuse (Hester et al. 2006), which is closely linked to craving (Rosse et al. 1993), a potent driver of drug consumption (O'Brien et al. 1998). Impairment in controlling attention away from drugs is correlated with relapse (Carpenter et al. 2006), suggesting that cognitive control over attentional bias

is an important factor in breaking drug habits. Currently, the anatomical connectivity underlying this is unknown. Prior anatomical studies have shown that the rostral dorsal caudate receives input from the parietal cortex (Cavada & Goldman-Rakic 1991). The parietal cortex has long been known to be central for visuo-spatial attention and movement. In particular, the inferior parietal lobule (IPL) has connections not only to visual perception and movement regions (e.g., visual cortex, frontal eye field [FEF]), but also to cognitive control regions (e.g., dorso- and ventrolateral prefrontal cortex [dlPFC, vlPFC]) (Cavada & Goldman-Rakic 1989a, 1989b). Critically, the dlPFC and vlPFC also send inputs to the rostral dorsal caudate. Previously, we have shown that the caudate contains critical nodes of convergent input from prefrontal regions, including the dlPFC and vlPFC (Haber et al. 2006; Averbeck et al. 2014). However, it is unknown whether these connections converge with those from the IPL. We hypothesize that the terminal fields of the projections of the IPL, dlPFC, and vlPFC form a node of convergence in the rostral dorsal caudate, supporting attention-mediated modulation of drug habit maintenance and relapse. Here, we examined the anatomical projections to the rostral dorsal caudate with retrograde tracer injections in nonhuman primates (NHP). We then compared this anatomical connectivity to resting-state functional connectivity MRI (fcMRI) of the rostral dorsal caudate in healthy human adults.

Methods: Two cases (Macaca fascicularis) with retrograde wheat germ agglutinin-horseradish peroxidase (WGA-HRP) injections in the left rostral dorsal caudate were examined to comprehensively identify cortical input regions from the whole left hemisphere of the cerebral cortex. Human cortical fcMRI maps were computed for a region of the left rostral dorsal caudate in 1,000 healthy human adults (mean age = 21.3yr, 42.7% male).

Results: Two independent cases of tracer injections in the rostral dorsal caudate revealed labeled, primarily deep-layer cells in the IPL, FEF, dlPFC, and vlPFC, indicating the convergence of their terminals in the striatum. A human fcMRI analysis showed correlations of the rostral dorsal caudate with the IPL, dlPFC, and vlPFC.

Conclusions: Control over attentional bias modulates craving and affects the occurrence of drug relapse. The dlPFC and vlPFC are central to various aspects of cognitive control, such as visuo-spatial working memory, response inhibition, and attention direction (Arnsten 2007). The IPL is clearly implicated in visuo-spatial attention, particularly in reorienting attention away from ongoing, goal-directed tasks toward unexpected or particularly salient stimuli (Corbetta et al. 2008). Each of these cortical regions is connected with one another, underlying a complex relationship mediating cognitive control over attentional bias. The present results from NHP anatomy and human fcMRI indicate that the projections of the IPL, dlPFC, and vlPFC form a node of convergent terminal fields in the rostral dorsal caudate. This circuitry may be the means by which cognitive control and visual attention integrate with midbrain dopaminergic inputs in the striatum to modulate drug habit maintenance. Future studies will examine the resting-state correlations between the rostral dorsal caudate and the IPL, dlPFC, and vlPFC, as well as measures of attentional bias, in addicted individuals.

Keywords: attentional bias, cognitive control, striatum, addiction.

Disclosure: Dr. Haber received speaker honoraria from Pfizer and Medtronic, Inc.

W267. Does the Brain Circuit which Modulates Neuroendocrine Responses to Psychological Stress Differ in Polydipsic and Nonpolydipsic Schizophrenia Patients? Does This Reflect a Generalized Stress Diathesis?

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Background: Schizophrenia patients with primary polydipsia (POLY) differ from those without primary polydipsia (nonPOLY) on diverse neurobiological, behavioral and physiologic measures as well as their response to novel therapies (i.e. oxytocin). These and other findings are consistent with the view that the two groups have different psychiatric illnesses (MBG, Schizophren. Res, in press). In particular, POLY exhibit enhanced neuroendocrine responses to psychological stress which are in marked contrast to the blunted responses seen in nonPOLY. This difference is associated with distinct structural deformations in POLY on the hippocampus (HIPP), amygdala (AMY) and hypothalamus (HYPO). Blunted responses in nonPOLY, in contrast, appear to reflect adaptations to the psychiatric disorder. Furthermore, projections from the HIPP to the underlying implicated segments of the AMY and HYPO normally modulate central and peripheral neuroendocrine responses to psychological stress. Projections from the HIPP to the medial prefrontal cortex (mPFC) and nucleus accumbens (NA), in contrast, modulate more generalized responses to stress and are also heavily implicated in the pathophysiology of schizophrenia.This study tests the hypothesis that I) hippocampal modulation of neural activity underlying neuroendocrine responses to psychological stress differs in POLY and nonPOLY, and II) this difference is part of a hippocampal-mediated stress diathesis in POLY. Healthy control subjects were also examined, and hippocampal modulation of other structures implicated in schizophrenia were determined (see d below) to establish specificity of the findings.

Methods: Seven POLY, nine nonPOLY and nine healthy controls underwent 2 seven minute rs-functional magnetic imaging scans. Seventeen ROIs (right and left (r/l) HIPP; r/l AMY, HYPO; r/l mPFC, r/l NA; and r/l thalamus, r/l pallidum, r/l caudate, r/l putamen) were identified with Free Surfer utilizing large deformation diffeomorphic metric mapping. BOLD signal attributable to motion, and artifact identified via isolation of the CSF and white matter signals, were removed. Next the Pearson correlation coefficient was calculated between the residual BOLD signal in each voxel in each of these ROIs with the signal in every other voxel in all 17 ROIs. Values for ROI pairs were averaged yielding 153 FCs per subject. The 33 FC with the HIPP were grouped into ROI pairs which included a) just the HIPP (n = 3); b) the AMY and HYPO (n = 6); c) the mPFC and NA (n = 8); and

d) the four other control structures noted above (n = 16). Data were analyzed with a hierarchical mixed model linear regression with subject at level 3, ROI pair at level 2, and FC value at level 1. FC in the grouped ROI pairs noted in a,b,c above were each contrasted to the 16 control ROI pairs in d (i.e. simple contrasts S1-S3). Subject group was also transformed to two Helmert contrasts to further preserve power (H1: HC to patients, H2: nonPOLY to POLY). Hypothesis testing was based on the interactions between the three measures of relative hippocampal connectivity and the two group contrasts.

Results: Motion parameters, outliers, the strength of all 153 FCs, and that of the 16 control FCs (i.e. d) were similar across groups. The relative strengths of (a) the 3 FCs within HIPP were similar across groups. The relative strength of c) HIPP connections to the NA and mPFC were greater in patients than controls ($Z = 1.96$, $P < .05$), but similar in the two patient groups ($Z = 1.31$ $P < .18$). Finally, as predicted b) the relative connection strength of the HIPP to the AMY and HYPO differed in POLY and nonPOLY($Z = -3.0$, $P < .003$).

Conclusions: Neuroactivity in the hippocampal circuit modulating neuroendocrine responses to psychological stress differs in schizophrenic patients with and without polydipsia. This finding supports other data indicating this circuitry contributes to a distinct psychiatric disorder in the polydipsic subset. The findings do not, however, indicate that this circuit disruption is part of a hippocampal-mediated stress diathesis.

Keywords: resting state fMRI, schizophrenia, subtypes, neurocircuitry.

Disclosure: Nothing to Disclose.

W268. Absence of Adenylyl Cyclase Isoforms AC1 and AC8 Blocks Opioid Receptor Activation of Serotonin, but Not Dopamine, Turnover and Unmasks an Effect on Striatal Glutamate and GABA

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Background: Activation of the Gi-protein-coupled mu opioid receptor (μOR) is a potent analgesic strategy but nonetheless with clinical limitations such as tolerance and addiction related behaviors after repeated opioid use. Typically μORs, located on nerve terminals, inhibit transmitter release potentially via the activation of inwardly rectifying K+ channels (GIRK). Additionally, behavioral studies in genetically modified mice indicate that the Ca++-dependent adenylyl cyclase isoforms 1 and 8 (AC1/8) are critical for the full expression of morphine tolerance, dependence, withdrawal, and reinforcement. Central monoaminergic systems (5HT, NE, DA) modulate acute and chronic pain processing and their activity is potently influenced by μOR, typically inhibiting GABA afferents to these systems. Using mice with a double knock out of AC1/8 (DKO), we tested whether the acute μOR-dependent activation of (supraspinal) 5HT and DA systems was dependent on the presence of AC1/8; moreover we used 1H-MRS ex vivo to determine potential effects on striatal glutamate and GABA.

Methods: Forty five min after treatment with saline or the μOR agonist fentanyl (25 ug/kg, sc), wild type (WT) or DKO mice were sacrificed and bilateral tissue punches (2-3 mg) obtained from coronal slices. Levels of monoamines and cognate metabolites in acid extracts were determined with HPLC-EC; magic-angle 1H-MRS (11.7T) was used to determine glutamate, glutamine, and GABA in intact tissue punches.

Results: Consistent with previous reports in rats, fentanyl increased 5HT turnover (5HIAA/5HT) in the anterior cingulate cortex (ACC), hippocampus (HC), and anterior dorsal striatum (AST) in WT mice ($p < 0.05$). In contrast, fentanyl had no effect on 5HT turnover in mice lacking AC1/AC8. Fentanyl also increased significantly striatal DA turnover (DOPAC/DA, HVA/DA) and this effect did not differ between genotypes. Genotype did not influence 5HT levels in saline treated controls. DKO animals showed a drug-induced decrease in the 1H-MRS-visible levels of glutamate (most likely in efferent nerve terminals from the ACC) and GABA (presumably in dendrites and recurrent collateral axons of medium spiny projection neurons).

Conclusions: The results support the notion that acute disinhibition of dorsal raphé 5HT neurons, subsequent to activation of μOR on GABA nerve terminals in the raphé, is critically dependent on AC1/8 isoform expression. Moreover, the absence of AC1/8 unmasked a μOR-induced decrease in striatal glutamate and GABA. This latter effect may reflect decreased corticostriatal excitation of GABA-containing MSN in the projection field of the rostral cingulate cortex. The μOR induced changes in the neurochemical profile may be associated with some of the unique behavioral phenotypes of DKO mice.

Keywords: serotonin, opioid, AC1 AC8 DKO, glutamate GABA.

Disclosure: Nothing to Disclose.

W269. Transient Increases in Expression and Function of the Plasma Membrane Monoamine Transporter (PMAT) May Contribute to Treatment Resistant Depression during Juvenile and Adolescent Periods

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Background: Depression is a devastating disease for which most patients are not effectively treated. This problem is compounded in children and adolescents where only two antidepressant drugs are currently approved for clinical use. Both belong to the selective serotonin (5-HT) reuptake inhibitor (SSRI) class of antidepressant, and act by blocking high-affinity uptake of 5-HT from extracellular fluid via the serotonin transporter (SERT). The therapeutic utility of SSRIs is thought to be triggered by downstream events that occur in response to their ability to increase extracellular 5-HT. However, our studies using adult mice show that the ability of SSRIs to inhibit 5-HT uptake is greatly limited by the presence of non-SERT, decynium-22 (D22) sensitive transporters for 5-HT. Thus, by preventing extracellular 5-HT rising to therapeutically useful levels, non-SERT

transporters provide a mechanistic basis for limited therapeutic efficacy of SSRIs. D22 inhibits activity of organic cation transporters (OCT1, OCT2 & OCT3) and the plasma membrane monoamine transporter (PMAT). Consistent with a role for these transporters in antidepressant response, we found in adult mice that D22 enhanced antidepressant-like activity of the SSRI, fluvoxamine, via an OCT3-dependent mechanism. Moreover, we found that D22 given alone produced antidepressant-like effects in SERT heterozygote (+/-) and SERT knockout (-/-) mice with constitutively reduced or absent SERT expression. In each case, increased antidepressant-like activity was positively correlated with increased inhibition of 5-HT uptake. Unknown is the role D22-sensitive OCTs and PMAT play in the regulation of 5-HT uptake during childhood and adolescent development, and importantly, unknown is their role in modulating antidepressant activity during childhood and adolescence. In addition, surprisingly little is known about SERT function and expression during these ages. The present studies begin to fill these knowledge gaps.

Methods: A combination of radioligand binding and western blotting using specific antibodies were used to examine expression of SERT, OCTs and PMAT. In vivo chronoamperometry was used to measure the contribution of SERT, OCTs and PMAT to 5-HT clearance in vivo. The tail suspension test was used to assay antidepressant-like activity of D22. Juvenile, adolescent and adult mice were 21 days postpartum (P21), P28-35 and P90-120, respectively.

Results: Our studies show that [3H]D22 binding in hippocampus of juvenile, adolescent and adult wild-type mice is markedly higher than [3H]citalopram binding to SERT, with the difference being greatest in adolescent mice. Moreover, compared to SERT+/+ mice, [3H]D22 binding was more than 2.5- fold higher in SERT+/- mice, suggesting that OCTs and/or PMAT upregulate to compensate for a constitutive reduction in SERT expression. This is of particular interest given the link between low expressing and/or functioning variants of the SERT gene and psychiatric disorders. Western blot analyses suggest that transient increases in PMAT during juvenile and adolescent periods drive the increased [3H]D22 binding observed at these ages, whereas OCT3 appears to be increased in adults. Moreover, unlike the case in adults, the rate of 5-HT clearance from extracellular fluid in hippocampus of young SERT KO mice was as efficient as that in SERT+/+ mice. Finally, D22 (by itself) produced robust antidepressant-like effects in P21 mice, but had no effect in adult mice.

Conclusions: Depression is a major problem, especially for young people because the few antidepressants that are available to treat children and adolescents are less effective than in adults. Data presented here support the idea that PMAT plays a more prominent role in 5-HT uptake during childhood and adolescence than in adulthood, and may be a useful target for development of new antidepressant drugs, especially in these young populations. In contrast, in adults we found that OCT3 in particular, plays an active role in 5-HT uptake and antidepressant-like response, which is especially apparent when SERT activity is pharmacologically or genetically decreased. Continuing studies will afford new insight into mechanisms regulating 5-HT uptake in brain during childhood and adolescence. Given the strong link between dysfunction in 5-HT signaling and many psychiatric disorders, depression being prominent among them, elucidating mechanisms controlling 5-HT uptake in children and adolescents compared with adults will further our understanding of the etiological bases for these disorders and importantly, will guide the development of improved treatments.

Keywords: Depression, Transporters, Adolescents, Antidepressant.

Disclosure: Nothing to Disclose.