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ABSTRACTS COLLECTION

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W1. Enhanced Molecular Senescence is Associated With Brain Microstructural Changes in Tracts Critical to Executive and Memory Performance in Late-Life Depression

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Background: There is growing evidence that the biological mechanisms of depression significantly overlap with those observed during the aging process, leading to an acceleration of brain and systemic aging in depressed individuals. In a previous study, we developed the SASP (Senescence-Associated Secretory Phenotype) index, which is a composite measure of biomarkers related to senescence processes and can be viewed as an indicator of systemic background molecular senescence. This study aims to evaluate the association between SASP index with structural brain changes and cognitive performance in older adults with major depression.

Methods: We included subjects from an ongoing cohort of older adults with major depression ($n = 66$) that underwent 3 T brain MRI scan and comprehensive neurocognitive assessment. SASP biomarkers were derived from proteomic panel measured by multiplex immunoassay, and the SASP index was derived the regression analysis from a previously published study.

Results: LLD had significant higher SASP index compared to healthy controls ($p < 0.01$). Greater SASP index was negatively correlated with information processing speed ($r = -0.31$, $p < 0.001$), executive function ($r = -0.27$, $p < 0.001$) and global cognition ($r = -0.25$, $p = 0.01$). Diffusion tensor imaging (DTI) showed that higher SASP index was related to lower FA and higher mean diffusivity in specific brain tracts (e.g., the cingulate bundle [FA, $r = -0.15$, $p = 0.04$; MD, $r = 0.50$, $p < 0.001$); and uncinate fasciculus [FA, $r = -0.31$, $p < 0.001$; MD, $r = 0.40$, $p < 0.001$]).

Conclusions: Our results demonstrate that MDD is associated with enhanced molecular and cellular senescence changes, manifested by higher SASP index. Enhanced molecular senescence changes contribute to structural brain changes in critical circuits related to episodic memory and executive function in older adults with depression. Finally, the dysregulation of senescence-related biological cascades can provide a molecular link between depression and accelerated brain and systemic aging across the lifespan.

Keywords: Late-life Depression, Senescence Associated Secretory Phenotype, Biomarkers, Diffusion Tensor Imaging (DTI), Microglia

Disclosure: Nothing to disclose.

W2. Cognitive Decline Precedes the Advent of Subjective Cognitive Decline [Impairment] in the Evolution of Eventual Alzheimer's Disease

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Background: In 1982 we published the Global Deterioration Scale (GDS) which described 7 major stages in the evolution of brain aging and the progressive dementia of Alzheimer's disease (AD), (Reisberg, et al., Am J Psychiatry, 1982, 139:1136-1139). Three of these stages occur prior to the advent of the dementia of AD. We coined the terminology "mild cognitive impairment" (MCI) for the GDS 3 stage, in which subtle cognitive deficits are evident in a clinical interview (see Reisberg, et al., Int. Psychogeriatr., 2008, 20:18-31, for a historical review). The GDS also identified an earlier, GDS 2 stage, in which older persons have subjective complaints of decline [impairment] (SCD [I]) in the absence of objective evidence of decline. In 2010, we showed that GDS stage 2 (SCD [I]) persons have a hazard ratio of decline of 4.5, after controlling for demographic variables and follow-up time, in comparison with healthy, GDS stage 1 persons free of complaints (Reisberg, et al., Alzheimer's & Dementia, 2010, 6:11-24). Herein we investigated whether cognitive decline precedes the advent of subjective cognitive decline [impairment].

Methods: Subjects from our 2010 publication with no subjective or objective cognitive decline [impairment] were selected (i.e., subjects at GDS stage 1). Per design, all of the subjects were healthy at baseline. Enrollment of these subjects extended from 1/1/1984 to 12/31/1997. Forty-seven subjects in GDS stage 1 were followed. All subjects were followed over intervals of ~ 2 years. Results were censored at the cutoff date of 12/31/2001. Thirty-six subjects had a final GDS rating which was ≥ GDS stage 2, and 11 subjects had a final GDS stage of 1. Cox proportional hazard analysis was used to identify baseline cognitive declines that predict the stage of subjective cognitive decline [impairment] or more severe stages, to determine whether cognitive decline precedes the advent of subjective cognitive decline [impairment] in the evolution of eventual Alzheimer's disease.

Results: Only older age is a univariate baseline predictor of high risk of decline to GDS stage 2 or higher ($p < 0.05$). Non-significant baseline predictors include gender, education, Mini Mental Status Examination (MMSE) total scores, Brief Cognitive Rating Scale total scores or individual axes, Hamilton Depression Scale (HDS) total scores, and Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) total or item scores at baseline. In multivariable Cox proportional hazard analysis, after controlling for age, gender, and years of education, the combinatorial psychometric deterioration score, derived from an equal weighting of the 9 tests included in the test battery, was a significant baseline predictor of high risk of decline ($HR = 1.74$, $p = 0.03$). HDS item 5, insomnia middle, is also a baseline predictor ($HR = 4.63$. $p = 0.009$). Also, of the 9 psychometric variables, after controlling for age, gender and education, high risk of decline is associated with lower scores on paragraphs, initial recall ($p = 0.037$), (from the Guild Memory Scale), digit recall, 22forwards ($p = 0.001$), and digit-recall, backwards ($p = 0.001$), from the Wechsler Memory Scale (Wechsler, 1945).

Conclusions: There is a stage of psychometric cognitive decline (PCD), which precedes the advent of the stage of subjective cognitive decline [impairment], in the evolution of eventual Alzheimer's disease.

Keywords: Preclinical Alzheimer's Disease, Subjective Cognitive Decline, Brain Aging, Subjective Cognitive Impairment, Psychometric Tests

Disclosure: Nothing to disclose.

W3.Glucose Metabolism and Amyloid in Elderly APOE4 Homozygotes.

Abstract not included.

W4. Targeting Dopaminergic Mechanisms of Slowing to Improve Late Life Depression

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Background: Depressive illness affects 8-25% of older adults, is a leading cause of morbidity/mortality in this population and is difficult to treat effectively. Decreased processing speed is common in late life depression (LLD), explains much of the functional disability associated with LLD, and strongly predicts antidepressant non-response. In addition to cognitive slowing, individuals with LLD also exhibit motor performance deficits (particularly slowed gait speed) that confer additional risk for falls, hospitalization, and death. One important cause of psychomotor slowing in LLD is the gradual and progressive reductions in dopamine levels, D1/D2 receptor density, and the availability of dopamine transporters (DAT) that occurs with aging. Reduced dopaminergic tone is associated with decreased processing speed as well as diminished motor performance. Dopamine agonists enhance cognitive and motor performance, whereas antagonists impair performance across a variety of tasks. Since slowed processing and gait speed predict the development of LLD and mediate much of the disability associated with LLD, the goal of this NIMH-funded R61 project was to evaluate pharmacologic augmentation of dopamine as a novel therapeutic strategy for LLD.

Methods: Adults aged > 60 years with a DSM 5 depressive disorder, significant depressive symptoms (Center for Epidemiologic Studies-Depression Scale > 10), and decreased gait speed (average walking speed over 15' course < 1 m/s) received 3 weeks of treatment with levodopa (L-DOPA) monotherapy. Each subject began taking 37.5 mg carbidopa/150 mg levodopa (1.5 25/100 sinemet tablets) once daily for one week, then increased to 75 mg carbidopa/300 mg levodopa for one week, and finally increased to 112.5 mg carbidopa/450 mg levodopa for one week. Depressive symptoms, processing speed, and gait speed were measured weekly, thereby assessing the effects of L-DOPA at 150 mg, 300 mg, and 450 mg doses. Subjects unable to tolerate prescribed dosage increases were maintained on the highest tolerable dose.

Pre- and post-L-DOPA neuroimaging was conducted with [11 C]-raclopride positron emission tomography (PET) using two different methods: (1) prior to treatment initiation following a single 300 mg test dose of L-DOPA or (2) at the end of the 3-week duration clinical trial following a 300 mg dose of L-DOPA. The L-DOPA effect was calculated as the percent change (BPND) following a 300 mg dose of L-DOPA. ΔBPND = 100% * [BPND (post-L-DOPA) - BPND (baseline)]/BPND (baseline). We followed standard procedures for measuring L-DOPA-induced changes in synaptic dopamine levels set forth in PET studies of Parkinson's disease patients. On the day of the post-L-DOPA scan, subjects were given 75 mg carbidopa/300mg L-DOPA, and the start of tracer injection was timed to coincide with the time of onset of L-DOPA effects (30 minutes following oral dose). Thus, the 60-minute PET scanning session occurred from 30 minutes to 90 minutes following L-DOPA dosing in all subjects. We hypothesized that treatment with L-DOPA would improve depressive symptoms in LLD by enhancing striatal dopamine neurotransmission and improving cognitive/motor slowing.

Results: N = 36 subjects having mean age 74.7 ± 7.5 (37% men) and Hamilton Rating Scale for Depression 16 ± 4.3 took at least one dose of study medication, with N = 15 of these subjects undergoing PET scanning. L-DOPA treatment was associated with dose-related improvements in processing speed (mean change and effect sizes [ES] for comparison of each dose vs. baseline on Digit Symbol Substitution Test: + 2.5 and d = 0.3 for 150 mg, + 4.6 and d = 0.5 for 300 mg, + 4.2 and d = 0.5 for 450 mg) and gait speed (mean change and effect sizes [ES] for comparison of each dose vs. baseline on time to walk 15 feet: + 0.01 and d = 0.04 for 150 mg, + 0.07 and d = 0.4 for 300 mg, + 0.11 and d = 0.6 for 450 mg). On average, subjects experienced 5.8 ± 6.4 HRSD points of improvement over the 3-week duration study.

N = 6 subjects PET scanned before and after a single 300mg L-DOPA test dose did not demonstrate significant [11 C]-raclopride displacement in the caudate or putamen. Subsequent subjects (N = 5 available for analysis to date) scanned before and after 3 weeks treatment with L-DOPA demonstrated 7-10% BPND reductions in the caudate and putamen bilaterally.

L-DOPA treatment was tolerated well, with N = 4 (11.1%) of subjects discontinuing study medication due to adverse events (nausea most frequent reported side effect [16.7%]).

Conclusions: In these LLD patients with significant psychomotor slowing, L-DOPA monotherapy was associated with moderate to large effect size improvements in processing speed, gait speed, and depressive symptoms. [11 C]-raclopride PET scanning of a subgroup of participants suggested subacute, but not single-dose, L-DOPA treatment was associated with increased tonic dopamine release in the caudate and putamen. L-DOPA treatment may represent a promising precision intervention for this high-risk and treatment-resistant subgroup of depressed older adults.

Keywords: Dopamine, Late-life Depression, Processing Speed, Gait Speed, Precision Medicine for Depression

Disclosure: Nothing to disclose.

W5. Steroid Hormones, Reproductive Aging, and Major Depression: Sex Differences in Memory Decline in Early Midlife

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Background: Major depression (MDD) is a risk factor for memory decline and Alzheimer's disease (AD). Women have twice the risk for MDD, which may be associated with higher frequency of AD in women vs. men, adjusted for longevity. Some mood circuitry regions are shared with memory circuitry, e.g., dorsolateral prefrontal cortex (DLPFC), hippocampus (HIPP), and paraventricular hypothalamic nucleus, thus functional deficits may be shared as well. MDD women may therefore be at higher risk for memory decline postmenopause. We previously demonstrated reproductive aging is associated with reorganization of functional working memory (WM) circuitry. Over menopausal transition, higher DLPFC and HIPP activity were associated with maintaining WM performance, suggesting less efficient DLPFC processing and failure to disengage HIPP. Controlled for age, this was significantly associated with lower estradiol levels, demonstrating greater impact of reproductive than chronologic age on WM. Better WM performance in healthy postmenopausal women was associated with higher levels of DHEAS, a weak adrenal androgen, in part, aromatized to estradiol. Here, we tested the hypothesis that in MDD vs. healthy women, lower estradiol and inability to compensate with DHEAS will be associated with less capacity to maintain intact memory function after menopause compared to pre-/peri-menopausal women and men.

Methods: 212 early midlife adults, equally divided by sex, underwent cognitive and fMRI assessments. STRAW-10 and serology determined pre-, peri and post-menopause stage. Gonadal hormones were measured by liquid chromatography-tandem mass spectrometry, and DHEAS by chemiluminescent Immunoassays. MDD was based on SCID interviews. Participants performed verbal WM tasks (N-Back) during fMRI, analyzed using SPM8. ROI analyses were based on anatomically defined HIPP and DLPFC masks, from which β weights were extracted for each person, dependent on WM load (2-back > 0-back). Face-Name Associative Memory and 6-Trial Buschke Selective Reminding Test (SRT) were used to assess memory.

Results: Variation in WM circuitry activity with reproductive aging in healthy women was primarily due to estradiol on DLPFC BOLD signal. In postmenopausal healthy women, higher DHEAS related to reduced (more efficient) DLPFC BOLD activity ($r = -0.45$, $p < 0.05$), resembling pre-/peri-menopausal women vs. men ($Z = -2.64$, $p < 0.01$), an effect not seen in MDD women. DHEAS had little impact on WM circuitry (e.g., DLPFC) or performance in MDD postmenopausal women. In contrast to healthy women, MDD postmenopausal women had significantly lower estradiol levels ($Z = -2.18$, $p < 0.05$) and increased BOLD activity in HIPP (failure to disengage; $Z = -1.94$, $p = 0.05$). Healthy men with higher bioactive testosterone had lower WM DLPFC BOLD activity and better WM performance.

Conclusions: DHEAS impacts WM circuitry and performance in healthy postmenopausal women, similar to effects of estradiol in pre-/peri-menopausal women. Impact of DHEAS was not present in MDD women. In fact, MDD vs. healthy women had lower levels of estradiol across reproductive stages. Deficits in WM circuitry associated with MDD, HPG axis, and inability of adrenal gland (HPA) to provide estrogenicity after ovarian decline may contribute to less ability with MDD to maintain intact memory function with age. Targeting WM and mood deficits earlier in life with neurosteroids may help to maintain intact memory later in life.

Keywords: Major Depression Disorder, Sex Differences, Menopause, Working Memory, fMRI

Disclosure: Nothing to disclose.

W6. Activity-Dependent Regulation of Fear Expression in Hippocampal-To-Prelimbic Cortex Projection Neurons

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Background: Several neuropsychiatric disorders, including generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD), feature dysregulation of fear as a core symptom. Brain-derived neurotrophic factor (BDNF) mediates activity-dependent synaptic plasticity and is associated with both GAD and PTSD and has been linked to fear regulation in animals and humans. Despite the known association between BDNF and fear-related behavior, the mechanisms by which BDNF regulates specific neural circuits to impact fear regulation are not entirely clear. To further address this question, we first investigated whether ventral hippocampal (vHC) neurons with direct projections to the prelimbic subregion (PrL) of the medial prefrontal cortex (mPFC) are necessary to mediate expression of learned fear in mice. We then investigated whether activity-dependent BDNF signaling selectively impacts vHC-PrL projectors during fear expression.

Methods: Fear expression was assessed by first conditioning mice to freeze in response to a tone paired with a foot-shock, then placing the mice into the conditioning chamber 48 h later to assess context and tone recall. To probe whether vHC-PrL projectors are associated with fear expression, we used a combination of retrograde viral labeling and c-Fos immunohistochemistry to label these neurons, and viral expression of an excitatory DREADD receptor to manipulate these neurons prior to fear recall. We used single-molecule fluorescence in situ hybridization to assess whether BDNF is enriched in vHC-PrL projectors, and used ex vivo slice preparations to compare synaptic physiology in these neurons between BDNF-deficient mutants and wild-type (w/t) mice. Finally, we investigated how disruption of BDNF in this circuit affects population dynamics during fear expression by using in vivo electrophysiology and calcium imaging during behavior.

Results: We found that mutant mice with selective disruption of BDNF production from activity-dependent promoter IV (-e4 mice) displayed increased freezing during fear recall relative to w/t mice ($n = 8$ per genotype, $p = 0.012$). We next found that a higher proportion of vHC-PrL projectors co-express c-Fos following fear expression compared to mice that did not receive a foot-shock during conditioning ($n = 8$ per group, $p = 0.011$). Projectors were highly enriched for exon IV-containing BDNF following fear expression in both w/t and –e4 mice, and projectors in –e4 mice showed a higher resting membrane potential ($n = 4$ per genotype, $p = 0.006$) and lower frequency of inhibitory post-synaptic potentials ($n = 4$ per genotype, $p = 0.034$) when compared to w/t projectors. Synthetic activation of projectors prior to recall decreased freezing in w/t mice ($n = 8$ DREADD, 20 control, $p = 0.007$), and increased freezing in –e4 mice ($n = 6$ DREADD, 9

control, $p = 0.035$). Finally, increased freezing in –e4 mice co-occurred with abnormal hippocampal-prefrontal oscillatory synchrony, and manipulation of projectors impaired population dynamics in the PrL during fear expression.

Conclusions: Our data suggest that BDNF signaling impacts the ability of vHC-PrL projectors to bi-directionally regulate fear expression. These results could lend insight into potential precision medicine approaches to treating fear dysregulation in neuropsychiatric disorders by selectively targeting BDNF-mediated signaling pathways in projection-defined hippocampal-prefrontal circuits.

Keywords: BDNF, Neuronal Activity, Fear

Disclosure: Nothing to disclose.

W7. Individual Differences in Catecholamine Signaling Modulate the Behavioral and Immune Responses to Stress: Translational Findings Supporting the Role of Inflammation in PTSD Risk

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Background: Alterations in catecholamine signaling pathways have been shown to modulate stress and immune responses. Heritable variation in peripheral and central catecholamine signaling is produced by a common functional polymorphism in the catechol-O-methyltransferase (COMT), with Val carriers exhibiting higher COMT function and greater degradation of catecholamines than Met carriers. The role of catecholamine function has predominantly been studied in terms of central changes in catecholamines, however catecholamines are also strong regulators of immune function in response to homeostatic challenge. Here we examined the role of heritable differences in catecholamine signaling and its effect on behavioral and immune response to severe stress across species. Since alterations in the immune system are observed in trauma-disorders such as posttraumatic stress disorder (PTSD) and catecholamines modulate immune signaling pathways, we hypothesized that the disruptions in catecholamine signaling regulate the inflammatory state and immune response to stress, playing a key role in the development of avoidance behaviors after trauma. To test these hypotheses, we examined the contribution of the functional mutation in COMT, COMTval158met, to modulate enduring behavioral and immune responses to stress.

Methods: In animals, a unique "humanized" COMTval158met mouse line was used, in which the mouse COMT is replaced with the human COMT gene with the Val or Met mutation. Male and female mice were exposed to predator stress or control condition ($n = 11$-18 per genotype/stress group). Enduring behavioral effects of stress were examined 1-2 weeks post stress. In a second experiment, animals ($n = 15$-23 per genotype/stress group) were treated with the toll-like receptor 4 (TLR4) agonist lipopolysaccharide (LPS) or saline and assessed > 1 week later for enduring anxiety-like behavior. In both stress and immune challenge experiments, brain tissue and blood (plasma) were collected for cytokines quantification. Two-way ANOVAs (genotype X stress or LPS) were performed. Finally, in a parallel human study we examined the role of COMTval158met on PTSD symptom development in Marines 3 months after returning from a combat deployment ($n = 1478$, European ancestry). Multivariate regressions were conducted for PTSD diagnosis, with the genotype and measure of combat exposure/deployment-related stressors as factors. Trauma history, PTSD symptoms before deployment, and principal component analysis (PCAs) were added as covariates.

Results: Val carriers exhibited increased enduring stress responses compared to Met/Met carriers in both humanized COMTval158met mice and in humans after combat exposure (genotype X trauma interaction: $p < 0.01$ and $p < 0.05$ in mice and humans, respectively). In male mice, Val/Val carriers had increased baseline CRP plasma levels and reduced anti-inflammatory cytokines as measured by IL-10 plasma levels. Val/Val mice also exhibited elevated CRP brain levels in response to stress. Increased IL-1β signaling was observed in stressed mice regardless of genotype. Val carriers also exhibited significantly stronger and enduring avoidance behaviors compared to Met/Met carriers weeks after inflammatory challenge (genotype X LPS interaction: $p < 0.05$). This higher response in Val/Val carriers was associated with elevated plasma IL-1β levels. Female Val carriers showed a similar enhanced response to predator stress, but no response to immune challenge was observed.

Conclusions: These results suggest that heritable variance in catecholamine signaling modulates the response to an acute trauma, as modeled by the predator stress or LPS challenge in COMTval158-met mice or in humans after a combat deployment, potentially through increased peripheral and central inflammatory signaling. Sex-dependent effects need to be investigated further, since the results suggest that additional mechanisms are involved in the response to stress in female mice. Overall, these findings support targeting the immune signaling pathways as a potential therapeutic for some trauma-disorder patients. Data suggesting a potential role of the dopamine D1 receptor in the modulation of the catecholamine-modulated immune response to stress will also be presented.

Keywords: Catecholamine, Posttraumatic Stress Disorder, Translational Research, Inflammation

Disclosure: Nothing to disclose.

W8. Single-Nucleus RNA Sequencing of Medial Prefrontal Cortex During Fear Extinction

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Background: Post-Traumatic Stress Disorder (PTSD) is a debilitating psychiatric disorder with profound social burden and few effective treatments. Fear extinction deficits are thought to contribute to PTSD pathogenesis. Research from animal models and from human neuroimaging studies implicate medial prefrontal cortex (mPFC), among other structures, as playing a crucial role in fear extinction memory formation. In rodent models of fear conditioning and fear extinction, driving activity of neurons within infralimbic cortex (IL) within the mPFC has been shown to be sufficient to extinguish previously encoded fear memories. The IL is a heterogeneous cortical structure, however, which contains many cell-types. The molecular signature of the cell-types which are necessary and sufficient for forming and consolidating fear extinction memories remain unknown.

Methods: We used single-cell nuclear sequencing (InDrops) to identify clusters of neurons in the mouse mPFC that exhibit immediate early gene (IEG) expression two hours post fear extinction ($n = 9$) when compared with home cage ($n = 7$) and fear conditioned ($n = 7$) animals. We have used fluorescent in situ hybridization (FISH) and immunohistochemical techniques to confirm markers for cell clusters found with single-cell nuclear sequencing. Retrograde viruses expressing Rpl10a-eGFP were also used to identify molecular signatures of projection neuron populations using translating ribosomal affinity purification (TRAP).

Results: We have identified over 20 distinct cell-type populations within the mPFC, including populations of glutamatergic neurons, GABAergic interneurons, astrocytes,

microglia, and endothelial cells. Many of these clusters express known cell-type specific markers. We have also identified populations of neurons with previously undescribed molecular signatures. Several neuronal clusters exhibit IEG expression (including Fos, Junb, Npas4, Egr1, Egr4, and Nr4a1). One of the clusters with strongest IEG expression after fear extinction upregulates plasticity-master regulator BDNF and also Ptgs2, a potential pharmacologic target for PTSD

Conclusions: We provide pilot data to begin construction of a comprehensive map of cell-types within the mouse mPFC. We have identified both known and uncharacterized cell-types. Some of these cell-types possess transcriptional signatures suggestive of activity during fear extinction. Follow-up studies will assess the functional role of these cell-types in the process of fear extinction formation and consolidation.

Keywords: PTSD, Single-cell RNA Sequencing, Fear Extinction

Disclosure: Nothing to disclose.

W9. Poster Withdrawn

W10. Exploring BDNF Val66Met Polymorphism and Extinction Learning-Based Treatment Outcome in OCD: A Pilot Study

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Background: A common single-nucleotide polymorphism (SNP) in the human brain-derived neurotrophic factor (BDNF) gene (Val66-Met; rs6265), has been reported to alter extinction learning in human carriers and knock-in mice with the SNP. Extinction learning is a major component of behavioral therapies for anxiety disorders, and medication thought to enhance extinction learning may facilitate CBT gains. Our recent, open-label pilot study in un-medicated Obsessive-Compulsive Disorder (OCD) subjects (N = 10), found that abbreviated cognitive behavioral therapy (CBT) (10 one-hour exposure sessions), delivered during the two weeks when ketamine putatively facilitates extinction learning, helps individuals maintain ketamine-related improvement. To refine our understanding of the role of BDNF, we performed a secondary analysis to explore whether the BDNF Val66Met polymorphism is associated with treatment response to either exposure-based CBT or to ketamine. Given the BDNF Met allele impairs activity–dependent BDNF secretion that is critical for extinction learning, we hypothesized that patients without the BDNF Met allele would have a better OCD outcome than BDNF Met allele carriers.

Methods: With IRB approval, 10 un-medicated OCD (DSM-5) outpatients (ages 18-55) provided written informed consent. Participants had at least moderate symptoms (score ≥ 16 on the Yale-Brown Obsessive-Compulsive Scale; YBOCS). Four subjects met criteria for comorbid major depression and one for dysthymia; all had mild-to-moderate depression. One subject met criteria for general anxiety disorder. DNA was extracted from blood using QIAmp DNA Blood Kit (Qiagen) and used as template for amplification of the BDNF genomic portion that harbors the BDNF Val66Met. PCR fragment was digested with restriction endonuclease NlaIII (New England Biolabs® Inc, Boston, MA), and resolved in 2% UltraPure™ Agarose (Invitrogen, Carlsbad, CA). Participants received a single 40-minute ketamine infusion (dose = 0.5 mg/kg) and then completed 10 h of exposure and response prevention treatment with a trained psychologist over two weeks. To assess maintenance of combined ketamine and CBT effects, patients were followed for an additional two-weeks. At baseline, 20, 90, 110, and 230 minutes post-infusion, patients rated their obsessional severity using the OCD visual analogue scale (OCD-VAS). At baseline and weekly for 4 weeks post-ketamine, an independent evaluator, blind to study design, evaluated the patient's OCD severity using the YBOCS (primary outcome measure). Treatment response was defined a priori as > 35% YBOCS reduction at week 2.

Results: Nine of the 10 participants completed the infusion. Most participants were of European ancestry (n = 7); two were of African ancestry and all but one described themselves as "non-Hispanic." Genetic analyses showed six had Val/Val polymorphism and three carried one or both Met substitutions. Baseline YBOCS scores were similar in Met carriers (median = 33; range 28-34) and Met non-carriers (median = 28; range 21-35). Eight of nine participants reported a rapid reduction in obsessive severity, as measured by the OCD-VAS, on the day of infusion. BDNF variation was not significantly associated with ketamine response on the infusion day. Two weeks post-infusion, only one of three Met carriers (33%) was a responder, compared with four of six Met non-carriers (67%). One-month post-infusion (after a 2-week follow up period), three of six Met non-carriers were responders (50%), versus none of the Met carriers.

Conclusions: In this first study examining the association between the BDNF Val66Met SNP and treatment response to ketamine and CBT in OCD, there were two main findings: (1) BDNF variation was not associated with acute ketamine response on the infusion day; (2) BDNF variation was associated with differential response rate to subsequent brief, two-week, exposure-based CBT. The first finding contrasts with a study of major depression reporting enhanced antidepressant effects in Met non-carriers compared to Met carriers. This contrast suggests that BDNF plays a different role in OCD. Our study's second result is consistent with Fullana and colleagues' report that BDNF variation was associated with OCD response to 20 weekly sessions of exposure-based CBT (36% response rate in Met carriers; 60% in Met allele non-carriers), suggesting BDNF-mediated extinction learning mechanisms influence exposure-based OCD outcomes. Of note, no Met carrier (vs. 50% of Met non-carriers) maintained a treatment gain in the study's follow-up period. Taken together, these findings also suggest that ketamine may provide only short-term relief to individuals with BDNF-mediated extinction learning deficits that impair their response to exposure-based CBT. In parallel, exposure-based CBT may maintain gains in individuals with intact BDNF-mediated extinction learning. Our study's limitations include open-label trial design, small sample size, and lack of randomization. Clinical predictors of ketamine response have been reported in studies of major depression; small sample size impacted our ability to examine clinical predictors of ketamine's effects in OCD in this pilot study. In this sample of convenience, we cannot rule out the possibility that ketamine carry-over effects influenced the results of post-infusion exposure-based CBT. If replicated, however, our BDNF allele genotyping may help guide personalization of treatment for extinction-based learning.

Keywords: Ketamine, CBT, BDNF, OCD, Extinction Learning

Disclosure: Blackthorn, Consultant, Allergan, Consultant, Rugen, Consultant

W11. Clutter Blindness as an Insight Proxy in Hoarding Disorder: A Hypothesis-Generating Study

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Background: Insight is a transdiagnostic aspect of neuropsychiatric illness with prima facie clinical relevance. Within the obsessive-compulsive and related disorders, degree of insight has been established by DSM-V as a diagnostic specifier. In obsessive-compulsive disorder and body dysmorphic disorder, insight reflects the conviction with which an obsessional thought is held and can be assessed in a standardized manner using established instruments. In contrast, for hoarding disorder, insight has been defined as the degree to which an affected individual recognizes their hoarding behaviors as problematic. While impairment of insight is reported to be both common and treatment-interfering in hoarding disorder, little evidence is available to characterize the nature or correlates of poor insight in affected individuals. Confounding attempts to study insight, the dominant measures of hoarding disorder severity are based on self-report. Current evidence is contradictory as to whether individuals with hoarding disorder may under- or over-report their symptoms or the impact of their disorder. In this study, we explored whether individuals using the Clutter Image Rating (CIR), a well-validated 9-point pictorial scale of clutter severity with proven test-retest reliability, accurately report their symptoms when compared to ratings generated during home visits by trained independent evaluators.

Methods: We analyzed data obtained from n = 51 individuals (average age 56.7 (range 24 - 75), 80.3% female) who presented voluntarily to screen for participation in a group therapy intervention for hoarding disorder. Individuals underwent clinical diagnostic interviews, a battery of self- and clinician-rated assessments including the CIR, the Saving Inventory-Revised (SI-R), the Hamilton Depression Rating Scale-17 (HDRS), the Early Life Stress Questionnaire (ELSQ), and the Chapman Revised Physical and Social Anhedonia Scales (RPAS and RSAS). A home visit then followed (average inter-assessment interval 29 days, range 0 to 100) during which a trained, independent evaluator completed the CIR. Self-rated (SR-) and independent evaluator (IE-) CIR scores for individual rooms were averaged for each subject. A two-tailed paired t-test was used to compare average SR- and IE- CIR ratings. A SR-IE CIR difference score was generated by subtracting the IE-CIR average from the SR-CIR average. This difference score was used as a dependent variable for correlation analysis with independent demographic and clinical assessment variables.

Results: Average CIR scores generated by self-report were lower than those generated by independent evaluators (3.64 vs 4.06, $t = 2.99$, $p = 0.004$). 26 individuals (51%) underreported their clutter by CIR when compared with IE ratings, with 18 (35%) under-reporting by 1 full point or more, and 4 individuals (8%) underreporting by more than 2 points on average, or by nearly half the average IE-CIR score. SR-IE CIR difference scores correlated with severity of clutter as per IE-CIR ($r = -0.56$, $p < 0.0001$), though not with severity as per SR-CIR ($r = 0.18$, $p = 0.22$). In our sample, SR-IE difference was not significantly correlated with a self-report measure of hoarding severity (SI-R), nor with depression (HDRS), early life trauma (ELSQ), physical or social anhedonia (RPAS, RSAS), age, or inter-assessment interval.

Conclusions: Discrepancies in reporting of clutter via CIR may reflect contextual, interpersonal, as well as potential neurocognitive factors; the voluntary, treatment-seeking population sampled in this study may further overrepresent for individuals with preserved insight. Nonetheless, our data suggest that a substantial proportion of individuals struggling with clutter underreport the severity of their clutter, and that subjective underreporting may increase as objective clutter severity increases. Our analysis affirms the critical importance of independent evaluation when individuals with hoarding disorder are assessed in research or clinical contexts. Additionally, given that visual processing deficits are negatively correlated with insight in body dysmorphic disorder, and that visuospatial memory and processing deficits have been observed in obsessive-compulsive and psychotic disorders, discrepancies of symptom report using visual representations of clutter merit further exploration as a proxy for impaired insight in hoarding disorder.

Keywords: Hoarding Disorder, Insight, Visual Information Processing, Clinical Subtypes

Disclosure: Nothing to disclose.

W12. Theta Burst Stimulation for Posttraumatic Stress Disorder

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Background: Posttraumatic Stress Disorder (PTSD) is a highly prevalent, chronic psychiatric disorder associated with marked occupational and social dysfunction, with significant psychiatric and medical comorbidity. Existing evidence-based treatments successful in the general population are only modestly successful in improving symptoms and function in Veterans, due to limitations both in terms of tolerability and maximal efficacy. Therefore, innovative interventions are sorely needed for Veterans with PTSD.

The application of non-invasive neuromodulation technologies is developing rapidly across neuropsychiatry. There is an established body of literature that supports the efficacy of non-invasive neuromodulation for treatment of depression, although excitement for this approach for PTSD has been tempered by lengthy administration times. Intermittent theta-burst stimulation (iTBS) is a relatively new, more rapid administration protocol that approximates specific neural firing patterns, and has preliminary evidence supporting its use in depression. Importantly, we currently have little data on whether changes in symptoms occur alongside improvement in quality of life/social and occupational function.

Methods: This study evaluated the potential of iTBS in PTSD (NCT02769312). We delivered 1800 pulses of sham-controlled iTBS daily for 10 business days to 50 Veterans with chronic PTSD (intent-to-treat = 25 per group). All participants could then continue to receive another 10 sessions of unblinded iTBS.

Our primary outcome measures were feasibility and acceptability, followed by changes in PTSD symptoms, quality of life, and social and occupational function at the end of the two-week double-blind phase; depressive symptoms were also assessed. Follow up analyses used mixed models to test whether active stimulation had superior outcomes compared to sham iTBS up to and including a one-month follow up visit. Resting state fMRI was acquired on a subset (n = 26) of participants to identify predictors of improvement to active stimulation.

Results: Randomization resulted in groups balanced on demographic variables and symptom severity. At two weeks, active iTBS produced significant improvement in social/occupational function (Cohen's $d = .39$; $p = .04$), alongside a statistical trend towards improvement in depressive symptoms ($d = -.45$; $p = .07$), compared to sham. We found moderate effect sizes ($d = -.34$) favoring active over sham stimulation on PTSD symptoms. Mixed model analyses indicated clinically meaningful superiority of active over sham iTBS on PTSD symptoms ($ds = -.5$ to $-.7$; $p < .001$), depressive symptoms ($d = -.45$; $p < .001$), and social and occupational function ($d = .9$; $p < .001$). Improvements generally occurred within the first week of active stimulation and were sustained through the one-month study endpoint, with minimal additional change (i.e., $|d|$ loss/gain < .2 through follow up).

Retention was high (84% completion rate); side effects were consistent with those expected during standard TMS. There were

no seizures. Blinding was successful, as participants were not able to accurately guess their group assignment (ChiSq = 1.43, p > .1). Neuroimaging analyses indicated that baseline resting state functional connectivity predicted clinical changes with active iTBS. PTSD and depression symptom reductions were associated with stronger (greater positive) connectivity within default mode network (DMN) subsystems, and with anticorrelated connectivity between the DMN and both the executive and salience networks (all FDR corrected p < .05).

Conclusions: To our knowledge, this is the first sham-controlled study of iTBS for PTSD. While the benefit observed is promising, the results require replication. Effect sizes were comparable to prior studies of repetitive TMS for depression. That the majority of clinical changes occurred in the first week of stimulation (i.e., a rapid response) indicates that future iTBS research should focus on the time course and optimal duration or "dose" of this form of stimulation. Consistent with prior TMS neuroimaging studies, our findings implicate an important role of DMN connectivity, and underscores that elements of "healthy" cross-network functional relationships are necessary for clinical improvement.

Keywords: Theta Burst Transcranial Magnetic Stimulation, Posttraumatic Stress Disorder, Resting State Functional Connectivity

Disclosure: Nothing to disclose.

W13. Effects of Depression and Social Anxiety on Electrocortical Response to Positive and Negative Monetary and Social Outcomes

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Background: Despite being highly comorbid, depression and social anxiety are associated with different neural response patterns to positive and negative feedback. Specifically, depression has been associated with a blunted neural response to rewards whereas social anxiety has been associated with an enhanced neural response. The neural mechanisms implicated in these alterations are often investigated in the monetary domain. Yet, interpersonal problems commonly motivate treatment seeking. Thus, there is a growing interest in evaluating the neural basis of reward processing in the social domain. Despite this interest, methodological discrepancies in tests of monetary and social reward paradigms have made the direct comparison of brain function across domains challenging. In addition, most studies contrast positive (e.g., winning money) and negative (e.g., losing money) valenced feedback, making it difficult to determine which condition contributes most to aberrant neural responding. Finally, none have disentangled the intrinsically rewarding experience of being right, which may be differentially impacted by discrete psychopathology symptoms, from obtaining positively valenced feedback. We developed novel electroencephalogram (EEG)-based monetary and social outcome paradigms matched on trial structure, timing, and feedback stimuli. Using these methods, we tested the effects of reward domain, outcome valence, and being right on brain function in late adolescents with a range of social anxiety and depressive symptoms. These differences were probed via an electrocortical event-related potential (ERP), the reward positivity (RewP) that indexes engagement of medial prefrontal cortex and striatum 200-300 ms following onset of rewarding feedback.

Methods: Late adolescents (N = 204; 130 females; 19.92 ± 2.50 years), with a range of social anxiety (30.9% clinical range) and depressive (27.9% clinical range) symptoms completed novel monetary and social outcome tasks while undergoing EEG. For the monetary task, a pair of doors appeared on the screen. On half of the trials there was a positive valence goal: correctly predict the door that will result in a monetary win (win trials). On the other trials, there was a negative valence goal: correctly predict the door that will result in a monetary loss (lose trials). Incorrect predictions resulted in a null outcome. The social task had identical attributes except doors were replaced with photos of age-matched peers. Participants were told that some peers had rated them after receiving a text of their picture. Positive and negative valence goals were to correctly predict which peer had liked (like trails) or disliked (dislike trials) them, respectively. Incorrect predictions resulted in a null outcome, reflecting that the purported peer never received a text. The RewP was scored as the mean amplitude from 225 to 300 ms following feedback at electrode Fz. ANOVA analyses tested relations between brain function, reward processing, and symptom severity.

Results: A 2 (Domain: monetary/social) x 2 (Valence: win or like/lose or dislike) x 2 (Outcome: correct/incorrect) interaction emerged ($F(1, 203) = 29.41$, $p < .001$) for the ERP response. This was driven by Outcome x Valence interactions in monetary ($F(1, 203) = 86.14$, $p < .001$, $\eta p2 = .30$) and social ($F(1, 203) = 6.32$, $p = .013$, $\eta p2 = .03$) domains. In the monetary domain, being correct on win-focused trials elicited a larger RewP than being incorrect, $F(1, 203) = 182.68$, $p < .001$, $\eta p2 = .47$. In contrast, for lose-focused trials, the RewP to being correct and incorrect did not differ, $F(1, 203) = 0.61$, $p = .44$, $\eta p2 < .01$. In the social domain, being correct on like-focused trials elicited a larger RewP than being incorrect $F(1, 203) = 164.35$, $p < .001$, $\eta p2 = .45$. Likewise, being correct on dislike-focused trials also elicited a larger RewP than being incorrect, $F(1, 203) = 164.35$, $p < .001$, $\eta p2 = .45$. Thus, being correct about whether someone does and does not like you elicits a greater RewP than being incorrect. Effects varied based on severity of affective symptoms. Across all trials, greater dysphoria symptoms were associated with a smaller distinction in RewP for being correct versus incorrect, $r(204) = -.20$, $p = .004$, whereas greater social anxiety symptoms were associated with a larger distinction, $r(204) = .20$, $p = .004$. Finally, a Domain X Valence X Outcome X Social Anxiety interaction emerged, $F(1, 201) = 10.49$, $p = .001$, $\eta p2 = .04$. There was a greater distinction in RewP between being correct versus incorrect about social dislike feedback in youth with more severe symptoms of social anxiety, $r = .16$, $p = .022$. No significant relations emerged for monetary win, loss or social like outcomes. All effects were stronger in female participants.

Conclusions: We provide initial support for a novel approach for comparing neural response to monetary and social reward. Moreover, results show a brain-based mechanism by which correctly predicting negative peer feedback may be intrinsically rewarding, and thus contribute to maintaining social anxiety symptoms. These effects are stronger in women, and suggest a biologically based, symptom-specific target for novel therapeutic intervention. There is a critical need for such targets since a significant number of young women with social anxiety fail to respond to treatment.

Keywords: Monetary Reward, Social Reward, EEG, Social Anxiety, Depression

Disclosure: Nothing to disclose.

W14. Anxiety and Depressive Symptom Prevalence in a Canadian Medical Cannabis Use Cohort

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Background: Cannabis is commonly used recreationally for its euphoric and relaxing effects. Although considered an illicit substance in many parts of the world, regulatory bodies in the Netherlands, and several US states have legalized medicinal and/or recreational use, with Canada moving towards legalization of recreational use in the fall of 2018. In Canada, cannabis for medicinal purposes (CMP) can be legally obtained from licensed producers for a myriad of medical conditions, with appropriate physician authorization.

Anxiety disorders are chronic conditions with a lifetime prevalence of 31.6%. They include social anxiety disorder (SAD), generalized anxiety disorder (GAD), panic disorder (PD) and specific phobias. These disorders are associated with significant burden for afflicted individuals, their families and society. While many established efficacious first-line treatments exist, including antidepressants and cognitive-behavioral therapy, 40–60% of patients continue to have residual, impairing symptoms while others are non-compliant or have difficulty accessing treatments. Given such limitations, individuals may seek alternative treatments and public sentiment surrounding cannabis' purported anxiolytic effects suggest that cannabis may fulfil this role.

The primary active components in cannabis are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The ratio of these cannabinoids varies greatly between strains of cannabis and consequently induce a wide variety of effects. Only small studies of synthetic cannabinoids or CBD have been examined in clinically anxious populations. Yet, many Canadians report using cannabis to alleviate self-reported anxiety.

Given that the cannabis plant is the most widely available and used form, studies of pure or synthetic cannabinoids are not sufficient proxies to illustrate cannabis' potential anxiolytic effects. Canadians are currently using cannabis for anxiety symptoms, but whether these individuals are treating state anxiety or symptoms of a clinical disorder remains unclear. With the scientific literature indicating cannabis as a non-evidence-based treatment for anxiety, mood and related disorders, this study examines the prevalence of cannabis use for anxiety, psychiatric symptom severity and CMP use behaviors in a sample of authorized Canadian medicinal cannabis users.

Methods: A sample of medical cannabis users completed an online annual survey sent to them by their licensed producer, Tilray. All respondents answered questions regarding primary illness and symptoms treated with CMP. Those who identified anxiety as one of their primary symptoms treated with CMP in the second question then completed validated self-report symptom severity scales to characterize psychiatric morbidity including the GAD-7, the Patient Health Questionnaire (PHQ-9), the mini Social Phobia Inventory as well as screening questions for panic disorder and agoraphobia, based on DSM-5 criteria.

Results: In total, 2032/3405 completed the survey. Within this sample, 888(43.7%) reported using cannabis for anxiety symptoms and completed all psychometric screening instruments. Respondents were primarily male (58.2%), married (36.1%), living in an urban area (43.6%) with a college education (32.2%). Based on screening scale cut scores, rates of probable anxiety and depressive disorders were high (generalized anxiety disorder: 45.6%, social anxiety disorder: 42.4%, major depressive disorder: 25.7%, panic disorder: 4.7%). In total, 63.4% met screening criteria for ≥ 1 disorder. Most (92%) felt that cannabis improved their anxiety symptoms; nearly half (49%) reported replacing a drug prescribed to them by their physician with medical cannabis. Close to half (42%) used 1-2 g of cannabis/day; 35% used < 1 g/day; 23% used ≥ 3 g/day. The severity of anxiety (GAD-7, $p < 0.001$) and depressive (PHQ-9, $p < 0.001$) scale scores was positively associated with the amount of cannabis used/day. Post-hoc comparisons revealed that high users (> 3 g/day) had significantly higher scores than moderate (1-2 g/day) or low users (< 1 g/day) (GAD-7,$p < 0.01$, PHQ-9,$p < 0.01$).

Conclusions: Nearly half of the CMP users in this sample reported using prescribed cannabis to treat anxiety symptoms and 2/3 met screening cut scores suggestive of a diagnosis of an anxiety disorder or depression. The vast majority felt that cannabis had improved their symptoms and denied symptoms suggestive of cannabis use disorder. Anxiety and depressive symptoms scores were higher in individuals smoking 3 g or more of cannabis per day.

Keywords: Cannabis, Adult Anxiety, Prevalence, Cannabis Use

Disclosure: Nothing to disclose.

W15. Towards Novel Treatments in the Anxiety Spectrum: Converging Evidence for a Role of Orexin Receptor Type 1 Variation in Panic Disorder, CBT Treatment Response and Fear-Related Intermediate Phenotypes

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Background: The orexin receptor type 1 (HCRTR1) has been implicated in arousal and fear learning by extensive preclinical studies, however, so far no work has focused on the effects of molecular HCRTR1 variation as part of a hypothesis-generating approach in the context of panic disorder with and without agoraphobia (PD/AG), PD/AG treatment response, and PD/AG-related intermediate phenotypes.

Methods: The HCRTR rs2271933 variant (Ile408Val, a cytosine [C] to thymidine [T] exchange in the protein's C-terminus region) was investigated in two independent PD/AG case-control studies (total n: 613 cases, 1,839 controls), as a predictor of exposure-based cognitive behavioural therapy (CBT) outcome ($n = 189$), for its trait impact on fear intensity measured with the Agoraphobic Cognitions Questionnaire (ACQ) ($n = 483$ patients, $n = 2{,}382$ healthy subjects), as a modulator of neuronal activity in a fMRI attention network task in healthy subjects ($n = 94$), and for its effect on exposure duration and heart rate response during a behavioural avoidance task (BAT) featuring agoraphobic conditions in PD/AG patients pre- and post-CBT ($n = 271$).

Results: HCRTR1 rs2271933 T allele carriers were significantly more likely to have a diagnosis of PD/AG in both case-control samples independently, and in their meta-analysis ($OR = 1.51$, $p = 4.2 \cdot 10\text{-}7$). Sex-specific analyses revealed a major driving effect in the female subsamples. Significantly poorer CBT outcome in clinical assessments (Hamilton Anxiety Rating Scale, [d] = 0.6, $p = 0.006$; Clinical Global Impressions Scale, $d = 0.7$, $p = 0.009$) as well as in PD/AG patient self-reports were linked to an increased T allele count. T allele carriers displayed higher ACQ scores in PD/AG as well as among healthy subjects. fMRI alerting network activation was decreased in T allele carriers in the inferior frontal gyrus and increased in the locus coeruleus, which also correlated positively with higher ACQ scores. Finally, increased exposure avoidance and initial heart rate response in the pre-CBT BAT and decreased post-CBT improvements in both readouts were discerned as a function of increased T allele loading.

Conclusions: The current results support the hypothesis of an involvement of molecular HCRTR1 variation in the pathogenesis of PD/AG and PD/AG-related traits, including significant effects on CBT treatment response, and encourage future evaluations of orexin receptor antagonists in approaches targeting a dysfunctional panicogenic arousal system in anxiety spectrum disorders.

Keywords: Orexin, Panic, Human Genetics, Anxiety Disorders
Disclosure: Nothing to disclose.

W16. Prospective Longitudinal Epigenome-Wide Association Study of the Development of PTSD in Traumatized ED Patients

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Background: Epidemiological studies worldwide have documented a high rate of exposure to traumatic events, including life-threatening accidents, rape, combat, physical violence, witnessing the death or injury of others and natural disasters. Such traumatic experiences significantly increase the likelihood of having post-traumatic stress disorder (PTSD). Most individuals who experience a traumatic event exhibit acute, but transient, symptoms and are widely experienced by most people over the first week after trauma and begin to resolve during the month. However, recovery from trauma occurs much more slowly in those with PTSD, such that symptoms are still present at one month and beyond. Risk factors such as female gender, history of childhood abuse, genetic susceptibility or lack of social support are useful for predicting which individuals may be most at risk following a traumatic experience, but there are currently few biological factors that can be used to monitor at risk individuals in real time. Recently, advances in epigenetics have provided insight into the molecular mechanisms that may contribute to the development of psychiatric disorders and symptoms following trauma exposure. Epigenetic modifications induce changes in gene expression through structural alterations of DNA that respond to changes in the environment, are potentially reversible and can be targeted for disease therapies. However, little is known the longitudinal epigenetic changes after trauma exposure or how they may differ in the month between a trauma and diagnosis of PTSD.

Methods: We recruited 26 subjects from the Emergency Department (ED) following a trauma exposure (~65% motor vehicle accident) that contributed 149 DNA samples longitudinally from the time of the trauma through 3 months post-trauma (Day 0, 1, 3, 7, 14, 21, first and three months). Of those that have completed the visits through 1 month, 34.6% meet criteria for PTSD diagnosis over the course of the study (Cases: N = 9, Age: 40.4 ± 9.6 y, M/F = 4/5; Controls: N = 17, Age: 35.1 ± 16.3 y, M/F = 12/5). There are no differences in sociodemographics (age, gender, race, education and income) or trauma history (childhood or adult history) among Cases and Controls, but Cases have higher depressive symptoms (BDI) at baseline (P = .04) and at 1 month (P = .04) following the index trauma. DNA samples were extracted from saliva and have excellent yields and quality. We have assayed DNA methylation using the MethylationEPIC BeadChip (Illumina). Of 149 samples run, only 1 failed QC due to low signal intensity. We next removed 1,527 probes that had missing data for > .1 of samples as well as 44,210 probes that are cross-reactive, 19,681 probes that are in X or Y chromosomes and BMIQ was used to normalize the probes. The final dataset contained 148 samples and 801,207 CpG sites. The proportion of buccal epithelial cells was estimated for each saliva sample and ranged from 32-74% (median 43%). We first evaluated the variability in methylation for each of the probes and found that 50% varied by at least 10% or greater. We tested for differences in methylation at each CpG site between Cases and Controls over the first month controlling for age, gender, proportion of buccal epithelial cells and chip position using the Edge package in R and controlled the false discovery rate (FDR) at 5%. We used MissMethyl to examine whether PTSD-associated CpGs (P < .05) can be organized into pathways (KEGG). For each of the CpG sites that change acutely over the first month with respect to PTSD status, we used linear regressions to characterize methylation at three months after the trauma.

Results: We found 30 FDR significant CpGs located on 23 genes that change over the first month (2.1E-6 < P < 2.2E-8). For example, methylation of cg10504927 located in the promoter region of ARPP21 (cAMP regulated phosphoprotein 21) increases over the first month with Cases compared to Controls (P = 4.7E-8); ARPP21 helps to regulate dopamine activity, particularly in the caudate nucleus and cerebellar cortex. Assessment of the nominally-associated CpGs (P < .05) revealed enrichment of 21 pathways (FDR < .05) including Glutamatergic synapse (P = .0009) and MAPK signaling pathway (P = .002), Axon guidance (P = .003), and Th17 cell differentiation (P = .003). Four of 30 CpGs (cg17061451: TULP3, cg06291266: NUDT21, cg14734794: LEP, cg15168017: PLCB4) continued to associate with PTSD (.04 < P < .006) in the cross-sectional analysis of subjects with follow up at three months, which is more than would be expected by chance.

Conclusions: In this longitudinal pilot study, we found significant DNA methylation changes in saliva that predict PTSD development following trauma exposure. Our results provide insight into the biological response to trauma and may reveal biomarkers that can be used to delineate those at risk for developing PTSD and those that will be resilient.

Keywords: Epigenetics, longitudinal, trauma, biomarker, DNA Methylation
Disclosure: Nothing to disclose.

W17. Conflict-Related Neural Activity Predicting Treatment Response in Unmedicated Adults With Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions (i.e. intrusive thoughts, images, or impulses) and compulsions (i.e. repetitive actions performed to prevent or mitigate distress). Exposure and ritual prevention (EX/RP) therapy is an effective, first-line treatment for OCD. While some resting state connectivity predictors of treatment response have been suggested, task-based functional markers are lacking. Herein, we sought to identify functional neural signatures that can predict response to EX/RP in OCD. Such signatures can identify neural circuits involved in treatment response and can be used to help guide and personalize treatment plans.

Methods: Unmedicated adult patients with OCD and healthy participants performed the Simon Spatial Incompatibility Task during high-resolution, multi-band fMRI (2 mm isotropic voxels, TR = 850 ms). Patients with OCD completed twice weekly EX/RP over the following eight weeks. OCD symptom severity was assessed using the Yale-Brown Obsessive-Compulsive Scale (YBOCS) at pre-, mid-, and post-treatment. Neuroimaging data from 36 patients and 33 healthy participants were preprocessed using the Human Connectome Project preprocessing pipeline and analyzed in grayordinate space. Conflict-related activity was extracted from 360 cortical parcels from the Glasser et al., 2016 atlas and from 14 subcortical regions. Linear mixed-effects models were used to identify brain regions that moderated the slope of change in YBOCS scores across treatment, allowing for missing data and controlling for age, sex, and IQ. False discovery rate was used for multiple comparisons correction.

Results: Of the 36 patients with OCD, 33 successfully completed treatment. Overall, YBOCS scores significantly decreased from pre-

to post-treatment ($t(32) = 8.54$, $p < .001$), with 23 showing > 35% reduction in symptoms. Conflict-related activity in 36 regions significantly predicted change in OCD symptoms (all ps < .05). These regions included the right pallidum and cortical parcels in the anterior insula, anterior cingulate, superior temporal sulcus, angular gyrus, and posterior cingulate. Greater conflict-related activity in all but one of these regions predicted greater improvement during treatment. To characterize the overall effect size of these associations, activity across these 36 regions was summarized using a principal components analysis. In a logistic regression, scores for the first principal component predicted which patients achieved wellness (YBOCS < = 12) after EX/RP ($B = 2.526$, $OR = 12.502$, $z = 2.640$, $p = .008$), controlling for age, sex, IQ, head motion, and baseline YBOCS scores. These scores discriminated patients who did vs. did not achieve wellness better than baseline YBOCS (AUC = 87.13% vs. 61.03%, $p = .02$). Additionally, though depression severity also tended to decline with EX/RP, activity in these regions did not predict change in depression severity (ps < .05), suggesting some specificity to OCD symptomology.

Conclusions: The current study used the most current methodologies in line with large-scale studies, such as the Human Connectome Project, to identify functional neural predictors of treatment response in unmedicated OCD patients. Most patients showed symptom improvements with EX/RP therapy, but responses varied across the sample. Conflict-related activity in cingulo-opercular and default mode regions was most predictive of treatment response. These findings suggest that cingulo-opercular and default mode circuits may be targets for novel treatments that augment the ability of persons with OCD to resolve cognitive conflict.

Keywords: OCD, Functional MRI (fMRI), CBT, Treatment Outcome Prediction, Conflict Monitoring

Disclosure: Nothing to disclose.

W18. Dimensional Fear is Associated With Reduced Cortical Thickness in Youth

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Background: The high comorbidity among anxiety disorders suggests that these disorders may share underlying neurobiological deficits. Abnormalities in structural measures such as cortical thickness have been demonstrated in adults with anxiety. Given that anxiety symptoms often manifest during childhood and adolescence, it is important to determine when these structural abnormalities emerge in youth. The purpose of this study was to examine the association between a dimensional measure of fear symptoms and cortical thickness within structural covariance networks.

Methods: We leveraged a sample of 1,394 male and female children, adolescents, and young adults imaged as part of the Philadelphia Neurodevelopmental Cohort. The fear dimension was constructed using a bifactor model of item-level data from a psychiatric interview. Cortical thickness was quantified using high-resolution MRI at 3 T. Structural networks were derived using non-negative matrix factorization, an advanced machine learning technique, and analyzed using generalized additive models with penalized splines to capture both linear and nonlinear developmental effects. To account for multiple testing across networks, we controlled the False Discovery Rate (FDR, $q < 0.05$).

Results: Increased fear symptoms were associated with reduced cortical thickness in the anterior and posterior cingulate cortex, the temporal-parietal junction, anterior insula, as well as orbitofrontal and temporal cortex (FDR-corrected p-values ≤ .04). Cortical thickness was specifically associated with fear, and it predicted fear symptoms above and beyond demographic characteristics and cognitive performance ($F(1367,1385) = 2.32$, $p = .001$). Interactions between fear and age, fear and sex, and age and sex were evaluated but found to be non-significant. In addition, we conducted sensitivity analyses to evaluate potentially confounding variables including race, maternal education, total brain volume, and psychotropic medication use. All analyses provided highly similar results.

Conclusions: These results provide novel evidence suggesting a common neuroanatomical phenotype that may underlie diverse anxiety disorders. Such results have implications for understanding how fear symptoms may shape long-term brain development and suggest potential biomarkers that could be used to enhance targeted, early interventions for fear symptoms in youth.

Keywords: Fear, Cortical Thickness, Brain development

Disclosure: Nothing to disclose.

W19. Oxytocin Modulates Intrusions and Neural Responses to Fear in a Human Trauma Model

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Background: There is conflicting evidence whether or not post-trauma administration of the neuropeptide oxytocin (OXT) could be effective in reducing post-traumatic stress disorder (PTSD)-like symptoms in victims of recent traumatic experiences (RTEs). In particular, the individual reactions following RTEs may be highly informative for assessing a potential clinical usefulness of OXT in early post-trauma therapeutic contexts.

Methods: In the present randomized controlled trial, 62 healthy women were exposed to the same experimental trauma (movie clip) twice 3 days apart and received intranasal OXT (24 IU) or placebo (PLC) over a period of 6 days. During this 6-day period, intrusive re-experiencing and trauma disclosure patterns were recorded using daily-life diaries, and neural responses to fearful faces were assessed with functional magnetic resonance imaging both after the first (i.e. before OXT treatment was commenced) and the second trauma exposure (i.e. after 3 days of treatment).

Results: In the PLC group, a higher frequency of intrusions correlated with less prefrontal cortex (PFC) activation and increased amygdala activation on response to fearful faces. There was no main effect of OXT treatment on re-experiencing, but exploratory analyses revealed that the peptide selectively reduced intrusions in those participants exhibiting a strong tendency to self-disclose their traumatic event. On the neural level, these behavioral effects of OXT were paralleled by increased PFC activation and enhanced functional PFC-amygdala coupling in response to fearful faces.

Conclusions: Collectively, our findings indicate that prolonged OXT treatment in combination with strong trauma disclosure may reduce trauma-induced intrusions by strengthening PFC-mediated top-down control of exaggerated amygdala reactivity. Our data thus emphasize the relevance of disclosure patterns in assessing the potential value of OXT in the prevention of PTSD.

Keywords: Oxytocin, Trauma Exposure, Functional MRI (fMRI)

Disclosure: Nothing to disclose.

W20. Toward an Integrative Model of HPA Axis Function Biomarkers in World Trade Center Responders

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Background: The response to the 9/11/2011 terrorist attack on the World Trade Center (WTC) was unprecedented in scope, involving tens of thousands of traditional (e.g., police) and non-traditional (e.g., construction workers) responders in rescue, recovery, and clean-up efforts. Posttraumatic stress disorder (PTSD) related to this event is both highly prevalent (about 14%) and persistent in WTC responders, even over a decade-and-a-half after 9/11. The present study aimed to fill a major gap in our understanding of the biology of this disabling condition, by conducting comprehensive evaluations of clinical, functional neuroendocrine, genotypic, gene x environment interaction, and molecular factors studied independently, as well as in concert, in a unique sample of WTC responders exposed to the same traumatic event and its aftermath.

Methods: Participants ($n = 375$) were selected via stratified random sampling from a diverse cohort of WTC responders attending periodic health monitoring visits at the WTC Health Program in the greater New York metropolitan area. Exposures to WTC-related traumatic events (e.g., handled human remains, injured while working for the WTC recovery effort) were assessed at responders' first health monitoring visit, on average 3 years after 9/11. WTC responders underwent an in-person, clinician-administered interview including the Structured Clinical Interview for DSM-IV (SCID-IV) and the Clinician-Administered PTSD Scale for DSM-IV (CAPS), on average of 15 years after 9/11. Participants spanned the full range of PTSD symptom severity, from no/low-symptom to severe, chronic WTC-related PTSD. Participants also completed the dexamethasone suppression test (DST) and blood draws to measure 8:00 am plasma cortisol levels, as well as collection of 24-hour urine samples to measure cortisol excretion. The Taqman method was employed to genotype FKBP5 rs1360780 and rs9296158 single nucleotide polymorphisms, and FKBP5 gene expression was measured in peripheral blood mononuclear cells (PBMCs).

Results: Preliminary analyses were conducted in a subsample with available data to date ($n = 318$). This subsample was an average 54 years of age, 82% male, 61% White, and comprised of 64% police and 36% non-traditional responders. When comparing WTC responders with current WTC-related PTSD (met past-month DSM-IV criteria and CAPS-IV ≥ 50) with those without lifetime WTC-related PTSD (never met DSM-IV criteria and lifetime CAPS-IV < 20), there was a significant main effect of group (current PTSD/no PTSD; Cohen $d = .38$), as well as a significant FKBP5 rs1360780 genotype x group interaction on post-dexamethasone cortisol suppression (Cohen $d = .40$). In post-hoc analyses, FKBP5 risk allele carriers (C/T or T/T genotype) with current PTSD exhibited higher post-dexamethasone cortisol suppression than C/C homozygotes with PTSD. Analyses with FKBP5 rs9296158 genotype yielded similar results. While 24-hour urinary cortisol levels were significantly lower in the current PTSD group (Cohen $d = .60$), they did not differ by FKBP5 genotype. In additional analyses, greater current PTSD symptom severity was significantly associated with higher FKBP5 gene expression in PBMCs, an effect that was moderated by FKBP5 rs9296158 genotype (A allele carriers $r = .28$). Finally, in preliminary multivariable analyses including demographic characteristics, childhood trauma severity, WTC-related exposure severity, post-dexamethasone cortisol suppression, 24-hour urinary cortisol, FKBP5 rs1360780 genotype, and FKBP5 gene expression, higher FKBP5 gene expression in PBMCs was significantly associated with greater current PTSD symptom severity ($\beta = .27$), with a magnitude comparable to that of childhood trauma severity ($\beta = .31$) and WTC-related exposure severity ($\beta = .30$). Analyses in the full sample of $n = 375$ participants will be presented at the ACNP meeting, additionally incorporating FKBP5 intron 7 methylation data and glucocorticoid receptor sensitivity in PBMCs into the multivariable model.

Conclusions: In preliminary analyses in this unique sample of WTC responders, FKBP5 genotype predicted differing post-dexamethasone plasma cortisol suppression in responders with WTC-related PTSD, and also moderated the association between PTSD symptom severity and FKBP5 gene expression in PBMCs. These findings suggest that FKBP5 polymorphisms may contribute to different biological subtypes of PTSD related to HPA axis function in trauma-affected WTC responders.

Keywords: HPA axis, PTSD, biomarkers, World Trade Center responders, FKBP5

Disclosure: Nothing to disclose.

W21. Increased Skin Conductance Response Hours After Trauma Predicts Future PTSD

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Background: Post-traumatic stress disorder (PTSD) is a complex and heterogeneous syndrome that can develop in 10-20% of trauma exposed individuals. A number of effective early interventions that can be deployed in Emergency Departments may eventually be effective in diminishing the development of PTSD symptoms following such traumas. However, limited access to these necessitates the ability to quickly identify individuals at the highest risk for developing PTSD. Robust predictors of risk in the immediate aftermath of trauma will lead to targeted use of evidence-based treatment and prevention of the disorder. Biomarkers that can quickly ascertain risk, independent of subjective self-report symptoms, demographic and cultural factors, are especially important for early intervention efforts.

One of the hallmarks of PTSD is increased psychophysiological arousal driven by the autonomic nervous system. Skin conductance response (SCR) to a psychological trigger of a previously experienced trauma offers a noninvasive, quantitative, biological output that is associated with current PTSD status and symptom severity. The objective of the study was to test whether a noninvasive mobile device that measures a physiological biomarker of autonomic nervous system activation could predict future PTSD symptoms.

Methods: Study participants ($n = 107$) were recruited as part of a large prospective study from the emergency department (ED) of Grady Memorial Hospital in Atlanta, GA, the largest Level 1 emergency department in Georgia (USA) after experiencing a DSM-IV-TR Criterion A trauma. Participants were followed for 1 year with PTSD symptom severity assessed at 1, 3, 6, and 12 months following the trauma.

To determine how many distinct latent classes best describe the trajectories of PTSD symptom severity based on PSS, a series of Latent Growth Mixture Modeling (LGMM) analyses was applied. Trajectories were based on the larger study sample (not all of

whom had SC measures) with at least one follow-up visit (N = 377).

Skin conductance response (SCR) was collected on 107 individuals during a standardized trauma interview in the ED using the eSense SC system within hours of trauma exposure. Follow-up data on PTSD status was collected at 6-months following the trauma.

Results: When determining trajectory outcomes, a three-class solution with fixed variance for intercept and slope was the best fitted model. The LGMM analysis resulted in three trajectories: a) chronic (11% of participants), b) recovery (33% of participants), and c) resilient (56% of participants).

SCR of participants in the chronic trajectory was significantly different on average from that of participants in the resilient trajectory $t11.927 = -4.310$, $p < 0.001$. There was a significant positive correlation between SCR in the ED and the probability of assignment to the chronic PTSD trajectory ($r = 0.489$, $p < 0.000001$) and a significant negative correlation with the resilient trajectory ($r = -0.377$, $p < 0.000001$). Lasso regression with elastic net was performed with demographic and clinical measures obtained in the ED, demonstrating that SCR was the most significant predictor of the chronic PTSD trajectory ($p < 0.00001$). The AUC for the ROC curve analysis for SCR on trajectory class assignment was 0.90 ($p < 0.00001$) with 95% confidence intervals of 0.80 and 0.99.

SCR was also significantly correlated with PTSD symptom severity at 6-months ($r = 0.41$, $p < 0.0001$). Average SCR was significantly greater in individuals who met DSM-IV criteria for PTSD compared to those who did not ($t83 = 3.866$, $p < 0.001$). Lasso regression with elastic net was performed with demographic and clinical measures obtained in the ED, demonstrating that SCR was the only significant predictor of the diagnosis of PTSD ($p = 0.004$). The AUC for the ROC curve analysis for SCR on PTSD diagnosis was 0.84 ($p < 0.0001$) with 95% confidence intervals of 0.73 and 0.94.

Conclusions: The current study is the first prospective study of PTSD showing SCR in the immediate aftermath of trauma predicts subsequent development of chronic PTSD. This finding points to an easily obtained, and neurobiologically informative, biomarker in emergency departments that can be disseminated in clinical settings to predict the development of PTSD.

Keywords: PTSD, Neurophysiology, Biomarkers for Risk Assessment, Skin Conductance Responses, Emergency Medicine

Disclosure: Nothing to disclose.

W22. Heterogeneity of PTSD Diagnostic Criteria: A Quantitative Comparison of DSM-IV, DSM-5, and ICD-11

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Background: PTSD diagnostic criteria have been criticized for permitting extremely high levels of heterogeneity (Galaztzer-Levy & Bryant, 2013). In DSM-IV, PTSD had one of the highest numbers of possible diagnostic combinations and disjoint combinations (sharing no symptoms). In DSM-5, both of these increased eightfold, with 636,120 possible diagnostic combinations and 336,000 possible disjoint combinations (Olbert et al., 2014). However, a recent study of DSM-IV diagnostic criteria showed that observed heterogeneity in empirical samples may be lower than theoretical levels (Olbert et al., 2014). The objectives of this study were to (1) replicate Olbert et al. for DSM-IV PTSD and major depression, (2) extend Olbert et al. to DSM-5 PTSD to determine if DSM-5 PTSD criteria increase observed heterogeneity, (3) test whether requiring a minimum cutoff on total severity score reduces heterogeneity, and (4) compare DSM-5 and ICD-11 PTSD criteria to determine if ICD-11's restricted symptom set reduces heterogeneity.

Methods: This study included three samples: DSM-IV undergraduates (N = 889), DSM-5 undergraduates (N = 1,926), and DSM-5 community sample (N = 439). Both sexes were included. All participants had unequivocal Criterion A exposure based on review of written trauma narratives. Items from the PTSD Checklist (PCL) were counted as a symptom if the item score was moderate and above. Heterogeneity was quantified according to Olbert et al. by counting the number of unique diagnostic combinations and disjoint pairs and by calculating the Jaccard coherence, combinatorial coherence, Gini-Simpson index, and normalized Shannon entropy. The 95% confidence intervals were calculated using a delete-one jackknife resampling method.

Results: Our results are summarized as follows (all $p < 0.05$): (1) PTSD is more heterogeneous than major depression. (2) DSM-5 PTSD is less heterogeneous than DSM-IV PTSD. (3) Requiring a minimum severity score reduces heterogeneity. (4) ICD-11 PTSD is less heterogeneous than DSM-5 PTSD but introduced some disjoint pairs. (5) ICD-11 PTSD had similar heterogeneity as DSM-5 PTSD when evaluated on all 20 DSM-5 symptoms. (6) An alternative six symptom diagnosis has similar heterogeneity as ICD-11 PTSD.

Conclusions: Our findings suggest that PTSD is heterogeneous but less so than theoretical levels suggest. DSM-5 PTSD criteria do not increase empirical heterogeneity despite the predicted eightfold increase. ICD-11 criteria reduced heterogeneity but not more so than an alternative criterion set of six symptoms rejected by ICD-11. PTSD heterogeneity can be mitigated by requiring a minimum total severity score. These findings should be replicated in large clinical samples, with data from a structured interview, and in samples with the same trauma type, similar demographics, and same subtypes.

Keywords: PTSD, Diagnostic Criteria, Heterogeneity, DSM-5, Nosology

Disclosure: Nothing to disclose.

W23. Reviewing a Revival of Psychedelics in Psychotrauma

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Background: Psychedelics have a long history in medicine. After the discovery of the psychedelic properties of LSD in the early 1950s, their use in psychiatry was explored. Results of these early investigations were mixed and often the studies suffered from poor design. Due to class I scheduling, the research into the therapeutic use of these substances was impeded, and definitive conclusions were never reached. Recently an urgency was addressed to advance the pharmacotherapeutic treatment of posttraumatic stress disorder (PTSD). Novel opportunities were needed to be addressed to 'prime the pump' for PTSD, with the focus on treatment-resistant illness. In looking into new methodologies, the focus has also moved to psychedelics.

Methods: This this review on recent research interest on PTSD and psychedelics we focus on 4 compounds: (2-chlorophenyl)-2-(methylamino) cyclohexan-1-one (ketamine), 3,4-methylenedioxymethamphetamine (MDMA), 2, O-fosforyl-4-hydroxy-N,N-dimethyltryptamine (psilocybin) and medicinal cannabis. All of these compounds have had a long history in medicine, are well known, and are frequently reported for a variety of psychiatric conditions. We reviewed literature on these 'old' known compounds and the rationale and possible effectivity in PTSD treatment.

Results: While these compounds were good for 10 studies in PTSD a decade ago, they now contribute significantly to over 100 studies. Most significant for ketamine, with a 10-fold increase in studies compared to a decade ago. Ketamine (0,5 mg/kg) is most known for indications other than PTSD but may have potential in exposure based treatment protocols. Empirical studies however are scarce. A template for sessions can be constructed: they follow a typical exposure-based approach. MDMA has seen a 5-fold increase in studies. MDMA (80-180 mg) has seen very promising effect sizes in recent studies. The FDA granted MDMA a breakthrough therapy designation for the treatment of PTSD, with phase III trials anticipated to begin in 2018. Typical is non-directive approach and long session times (6-8 h). The mechanisms underlying both MDMA and ketamine effects indicate memory reconsolidation modulation as a hypothetical process underlying its efficacy. Medicinal cannabis has also seen a 10-fiold increase in studies and is increasingly popular in research. The indication is nightmares and sleep related problems but may stretch to irritability and PTSD in general. It is not well known what the differential effects of CBD and THC are in patients with PTSD. Psilocybin is least well studied, tested for alcoholism, smoking cessation, and in patients with advanced cancer with anxiety. Psilocybin is a classic psychedelic and more hallucinogenic than the other reviewed compounds While safety and tolerability is well addressed, with exception for MDMA clinical studies in PTSD are still scarce. All drugs are also known in recreational setting.

Conclusions: There is exponential growth in studies on psychedelics in PTSD. Research studies are not conclusive on the efficacy but demonstrate an interest on their usefulness for PTSD. Each of these compounds is different in use and they all have different constraints on the clinical process. These drugs are propagated as adjuncts or catalysts to psychotherapy, rather than as stand-alone drug treatments. This may be different for cannabis as this may have symptom-based effects on sleep and irritability and is recommended for daily use. The model of medication-assisted psychotherapy is a possible alternative to existing pharmacological and psychological treatments in psychiatry. It is typical that few sessions are required to realize long lasting effects. Preliminary findings suggest that the effect of these medication-assisted psychotherapies extends beyond specific PTSD symptomatology and alters personality structure, resulting in long-term persisting changes. MDMA is most advanced in terms of published studies with robust effect. When properly applied, according to published manualized treatments, psychedelics may have potential in PTSD. We identify differences in uses and outline an agenda for research since these studies may contribute to novel and rational development of drug-assisted approaches to PTSD. Further research is needed to fully assess the potential of these compounds in the management of a complex disorder like PTSD. Of note may be that expanded research may lead to potential breakthroughs in brain disease knowledge of PTSD.

Keywords: PTSD, Pharmacotherapy, MDMA, Ketamine, Psilocybin

Disclosure: Nothing to disclose.

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W24. Effects of MDMA, as Compared to Methamphetamine, on Responses to Social Stimuli

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Background: This study examined the "prosocial" effects of ± 3,4-methylenedioxymethamphetamine (MDMA) in healthy adults, and compared these to a prototypical stimulant, methamphetamine (MA). MDMA is a stimulant with many amphetamine-like effects, but in addition, reportedly produces feelings of empathy and closeness with others. MDMA increases social behavior in preclinical models, and it is being studied in clinical trials to treat disorders related to social dysfunction (e.g., PTSD). The uniquely prosocial effects of MDMA may be related to its distinctive actions on serotonin or oxytocin. Here we examined the effects of MDMA and MA on two dimensions of social processing; i) affective responses to social touch, and ii) visual attention to faces expressing emotion. We hypothesized that MDMA, but not MA, would selectively enhance positive affective responses to social touch, and enhance visual attention to faces expressing positive emotions.

Methods: Healthy adult volunteers (N = 36) attended four sessions in which they received MDMA (0.75 or 1.5 mg/kg), MA (20 mg), or a placebo in randomized order under double-blind conditions. Participants completed two validated social processing tasks; a social touch task and an emotion reactivity task, using both self-report and electrophysiological measures. In the social touch task, participants rated the pleasantness of forearm brushing at both fast (30 cm/s; nonsocial) and slow (3 cm/s; social) speeds, while facial electromyography (EMG) was recorded. In the attention bias task, participants viewed faces expressing an emotion or a neutral expression, and electrooculography (EOG) recordings assessed the number of gazes toward each expression type.

Results: As expected, slow touch was rated as more pleasant than fast touch. Both doses of MDMA, but not MA, enhanced ratings of pleasantness of experienced touch at the slower, "social," frequency. The higher dose of MDMA also increased zygomatic muscle reactivity in response to both slow and fast touch. MDMA, but not MA, enhanced attention to happy faces, and the higher dose of MDMA also reduced attention to fearful faces.

Conclusions: These results extend our understanding of how MDMA enhances the experience of positive social interactions, i.e., by increasing the pleasantness of physical touch and increasing initial orienting to positive emotional faces. At higher doses, MDMA may also act to reduce responses to negative affective stimuli. These results distinguish MDMA from the prototypic stimulant MA, which does not influence affective responses in these ways. The prosocial effects of MDMA may contribute to its effectiveness as an adjunct to psychotherapy in the treatment of PTSD and other disorders of socio-emotional processing.

Keywords: MDMA, Social Behavior, Methamphetamine, Facial Emotion Processing, Somatosensory Processing

Disclosure: Nothing to disclose.

W25. Evaluation of Nociceptin/orphanin Fq (NOP) Receptor Antagonists in a Rodent Model of Traumatic Stress

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Background: Current FDA-approved pharmacotherapies for the treatment of post-traumatic stress disorder (PTSD) are limited in number and efficacy, and more pharmacological approaches are needed to improve patient outcomes. Recent evidence implicates the nociceptin/orphanin FQ (NOP) receptor system in PTSD, including a single-nucleotide polymorphism within the OPRL1 gene encoding the NOP receptor and effects of NOP agonists/antagonists on centrally-mediated processes known to be impaired in PTSD.

Methods: In order to understand potential utility of this class of compounds in remediating the effects of traumatic stress exposure, we characterized baseline effects on pain and behavioral performance. The NOP antagonists J-113397 and SB-612111 were tested at a range of doses to determine effects on pain sensitivity and exploratory and anxiety-like behaviors in male rats. The hot plate test was used to determine pain sensitivity, and the elevated plus maze and open field test were used to characterize general motivated behavioral changes. Controls were treated with vehicle solution.

Results: We found that neither NOP antagonist tested had significant effects on baseline measures in the hot plate, open field, elevated plus maze and acoustic startle tests. Importantly, we did not observe adverse effects in the selected dose ranges with the present behavioral assays and general observation.

Conclusions: We determined that adverse behavioral side effects are unlikely to confound behavioral pharmacology screening of NOP antagonists. Studies are now in progress to characterize the effects of these antagonists on recovery of exploratory and anxiety-like behaviors after a single-day sequential exposure to three predator species (snake, ferret and cat) to model traumatic stress. A complementary study is ongoing to evaluate the effects of NOP antagonism on the extinction of conditioned fear responses using inhibition of appetitive behavior. Together, these studies of threat and memory will facilitate understanding of the therapeutic potential of compounds targeting the NOP system for the treatment of PTSD.

Disclaimer: Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted under an approved animal use protocol in an AAALAC accredited facility in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NRC Publication, 2011 edition.

Keywords: Behavioral Pharmacology, NOP receptor antagonist, PTSD

Disclosure: Nothing to disclose. This work was supported by the US Army Medical Research and Materiel Command Military Operational Medicine Research Program and the National Research Council Fellowship Program.

W26. Rapid Anxiolytic Effects of a Serotonin Type 4 Receptor Agonist Involve Prefrontal Cortex-Brainstem Neural Circuit Recruitment

Abstract not included.

W27. Cortical Arousal and Pupillary Fluctuations in a Mouse Model of Acute Stress

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Background: Although pupillary responses to threat have been studied as a biomarker in PTSD, the fluctuations of the resting pupil have not. Across the cerebral cortex, neurons increase their firing when the pupil dilates, likely in response to locus coeruleus activity. By recording only, the pupil, the global arousal state of neurons throughout the cortex can be inferred. We hypothesized that the cortical dynamics might show altered dynamics after stress in mice, and that the pupil might serve as a potential biomarker for stress-induced hyperarousal

Methods: We recorded resting pupillary fluctuations in mice while they ran on a spinning disc before and after stress ($n = 8$ stressed, $n = 7$ unstressed). Pupillary fluctuations were quantified via spectral analysis and were also fit to a Hidden Markov Model (HMM) describing transitions in pupillary state. In a separate cohort, we recorded from neurons in the medial prefrontal cortex (mPFC) using microendoscope calcium imaging while simultaneously monitoring pupillary fluctuations ($n = 258$ stressed, $n = 316$ unstressed neurons). We estimated correlations between neurons and pupil, coherence at varying frequencies between neurons and pupil, and the relationship of neural activity to transitions in inferred pupillary state (using the HMM).

Results: Acute traumatic stress causes more rapid transitions between pupillary states ($p < 0.05$). These rapid transitions in the pupil reflect shifts in cortical arousal. Population (average) mPFC activity is highly correlated to the pupil ($r2 = 0.56$), but the neuron-pupil correlation is reduced by stress ($p < 0.001$). mPFC neuron-pupil coupling is particularly reduced at low frequency (< 0.5 Hz) after stress ($p < 0.05$). The relationship between individual pupillary states and mPFC activity is unchanged after stress – instead suggesting that the underlying state switching behavior underlies reductions in neuron-pupil coupling.

Conclusions: Rapid cortical arousal switching after stress can be inferred from an easily accessible external measurement. Slow fluctuations in pupillary diameter define epochs of high and low activity of mPFC neurons. A novel method of analyzing the resting pupil is presented, which could be used in translational studies of human PTSD. The underlying mechanism causing shifts in pupil-neuron coupling after stress is unknown, although the locus coeruleus is known to both cause pupillary dilation and also projects strongly to mPFC.

Keywords: Arousal, Pupillometry, In Vivo Calcium Imaging, Medial Prefrontal Cortex, PTSD

Disclosure: Nothing to disclose.

W28. Social Status-Dependent Effects of Fluoxetine on Socioemotional Behavior and Serotonin Neurochemistry in Female Rhesus Monkeys

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Background: Social interactions in most mammalian species are governed by hierarchical dominance relationships that are maintained by agonistic interactions that include aggressive behaviors. While social dominance is associated with a resistance to social stress and social subordination with stress-susceptible

phenotypes, the neural mechanisms that underlie social dominance and aggression remain unclear, especially in females. Data from hamsters indicate fundamental differences in the neural mechanisms regulating the expression of aggression and attainment of social dominance in males and females, such that hypothalamic vasopressin pathways are more important in males, and serotonin (5HT) pathways are more important in females. The current study assessed the effects of increasing 5HT activity by administering fluoxetine, a selective serotonin reuptake inhibitor (SSRI) used to treat depression and anxiety disorders in humans, on rates of socioemotional behavior (including agonistic, affiliative, and anxiety-like behaviors) and 5HT neurochemistry in a translational model of social dominance in female rhesus monkeys. We hypothesized that fluoxetine would increase rates of aggression and prefrontal and hypothalamic 5HT1A receptor binding potential (5HT1AR-BP) in dominant but not subordinate female monkeys.

Methods: Social subordination in socially housed female rhesus monkeys is a well-established model of chronic psychosocial stress in females. Subjects were gonadally intact adult female rhesus monkeys ($n = 14$; average age 13.5 ± 0.5 years) housed in small social groups of four to six females each (6 dominant and 8 subordinate females). We conducted a randomized, counterbalanced crossover study wherein subjects received both a 14-day treatment with fluoxetine (SC dose of 2.8 mg/kg/day) vs. vehicle (50% polyethylene glycol in sterile saline). A three-week washout period separated each treatment period. During each treatment period, standardized assessments were conducted. Behavioral observations were collected every two days using a standard monkey ethogram. On Days 7-10, an acute stress test was done to assess cortisol reactivity. On Day 15, a PET scan for 5HT1AR-BP was conducted using 4-(2′-Methoxyphenyl)-1-[2′-(N-2′′-pyridinyl)-p [18 F]fluorobenzamido]ethylpiperazine, and CSF samples were collected for assessment of central 5-hydroxyindoleacetic (5HIAA). Structural MR images were obtained within three weeks of the PET scan for co-registration of PET and calculation of 5HT1AR-BP. The Emory University Institutional Animal Care and Use Committee approved all procedures in accordance with the Animal Welfare Act and the U.S. Department of Health and Human Services "Guide for Care and Use of Laboratory Animals."

Results: Aggression emitted was influenced by a status by treatment interaction ($p = 0.05$, $\eta 2 = 0.27$), with fluoxetine enhancing aggression in dominant females and decreasing aggression in subordinate females. Subordinate females emitted significantly higher rates of submission behavior than did dominant females regardless of treatment ($p = 0.001$). Affiliation was influenced by a status by treatment interaction ($p = 0.05$, $\eta 2 = 0.27$), as fluoxetine treatment decreased affiliation in dominant females and increased it in subordinates. Anxiety-like behavior was also influenced by a status by treatment interaction ($p = 0.011$), as anxiety-like behaviors were reduced only in subordinate females ($p = 0.012$). CSF 5HIAA concentrations were reduced by fluoxetine ($p < 0.001$) regardless of social status. 5HT1AR-BP in the frontalorbital cortex was affected by a status by treatment interaction ($p = 0.005$), with fluoxetine reducing frontalorbital cortex 5HT1A-BP in dominant ($p = 0.015$) but not in subordinate females ($p = 0.069$). 5HT1AR-BP in the medial (mPFC) cortex was decreased by fluoxetine in dominant females ($p = 0.002$) but not in subordinate females ($p = 0.59$). Fluoxetine reduced lateralorbital cortex 5HT1AR-BP in dominant females ($p = 0.033$) but had no effect on lateralorbital cortex 5HT1AR-BP in subordinates ($p = 0.58$). Fluoxetine decreased 5HT1AR-BP in the hippocampus ($p = 0.044$, $\eta 2 = 0.30$), regardless of social status. In dominant females, frontalorbital and lateralorbital 5HT1AR-BP during fluoxetine treatment was associated with aggression ($r = -0.91$; $p = 0.013$) and anxiety-like behavior ($r = 0.88$; $p = 0.024$), respectively. In subordinates, mPFC 5HT1AR-BP during fluoxetine treatment was associated with affiliation ($r = -0.76$; $p = 0.029$), and frontalorbital ($r = -0.88$; $p = 0.004$), lateralorbital ($r = -0.79$; $p = 0.021$), and mPFC ($r = -0.846$; $p = 0.009$) 5HT1AR-BP were associated with anxiety-like behavior.

Conclusions: Taken together, the data show that increased 5HT activity following fluoxetine treatment in female monkeys alters socioemotional behavior and prefrontal 5HT1A-BP in a status-dependent manner. A future replication study will determine whether fluoxetine has opposite, status-dependent effects on 5HT1AR-BP and socioemotional behavior in male rhesus monkeys. The presence of sex differences in fluoxetine-induced changes in aggressive behavior typically associated with social dominance and stress resistance would suggest that serotonergic drugs may be more effective for increasing stress resistance in females but not males.

Keywords: Serotonin 1a Receptor, Female, Aggression, Fluoxetine, Social Status

Disclosure: Nothing to disclose.

W29. Behavioral Effects of Dasotraline Vs. Methylphenidate in an ADHD-Animal Model: Implications for Treatment of ADHD

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Background: Current ADHD pharmacotherapies have either limited efficacy or are associated with undesirable adverse events. Accordingly, there is an urgent need to develop novel pharmacotherapies with superior efficacy and tolerability profiles over current therapies for improved treatment of ADHD and related disorders.

Methods: We examined the effects of 3 doses of dasotraline (0.3, 1 and 3 mg/kg) vs 3 doses of methylphenidate (MPH; 0.3, 1 and 3 mg/kg) on locomotor activity in juvenile animals lesioned with 6-OHDA as neonates, an ADHD animal model, in comparison with sham-lesioned control age littermates. Developing animals (PD 25-28) were placed in locomotor cage 60 min after oral administration of vehicle or individual doses of tested drugs. Motor activity was monitored individually for 90 min in a microcomputer controlled infrared photobeam activity monitoring system.

Results: Lower doses of dasotraline (0.3 and 1 mg/kg) induced mild stimulation in locomotor activity (2.3- and 3-fold increase, respectively) in sham-lesioned juvenile animals. In contrast, the three doses of MPH (0.3, 1 and 3 mg/kg) induced profound and dose-dependent increase in locomotor activity (3.5-, 6.7- and 10.7-fold, respectively) over vehicle-treated animals. Young animals [PD 25] lesioned with 6-OHDA as neonates displayed significant and sustained lomocotor hyperactivity throughout the testing session. Administration of the three doses of dasotraline (0.3, 1 and 3 mg/kg) dose-dependently reduced locomotor hyperactivity (by 48%, 66% and 78%, respectively) in 6-OHDA-lesioned animals. Similarly, the three doses of MPH dose-dependently reduced locomotor hyperactivity (by 27%, 42% and 88%) in 6-OHDA-lesioned animals. When comparing dasotraline to MPH, the lower doses of dasotraline (0.3 and 1 mg/kg) were significantly more potent than the same doses of MPH in reducing total locomotor hyperactivity in 6-OHDA lesioned animals.

Conclusions: Lower doses of dasotraline (0.3 and 1 mg/kg) are more effective than comparable doses of MPH in reducing hyperactivity in 6-OHDA lesioned animals. In addition, the lower doses induced milder stimulation of locomotor activity than similar doses of MPH. These findings suggest that lower doses dasotraline may be more effective clinically than MPH in managing the symptoms of ADHD, and with superior tolerability profile including lower incidence of abuse potential. These

findings support the development of dasotraline as a novel medication for ADHD, with superior efficacy, safety and tolerability compared to MPH [supported by Sunovion Pharmaceuticals, Inc].

Keywords: ADHD, Dasotraline, Methylphenidate

Disclosure: Sunovion Pharmaceuticals, Grant

W30. Adolescent Stress Alters FKBP5 - Glucocorticoid Receptor Interactions in the Adult Hippocampus of Female, but Not Male, Rats

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Background: While exposure to stressors can be harmful throughout the lifespan, adolescents may be particularly vulnerable to the harmful effects of chronic stress exposure, and the consequences of chronic stress exposure may be sex-specific. In a rat model, chronic adolescent stress (CAS) increases depressive-like behavior in adult female, but not male, rats. Though behavior in adulthood has been found to be impacted by prior exposure to stressors during adolescence, the underlying molecular consequences of CAS in the adult brain are not fully characterized. This study assessed the extent to which CAS impacted regulation of the glucocorticoid receptor (GR) in a sex-specific manner in adulthood. Localization of the GR is impacted by interaction with co-chaperones, and specifically by FKBP5, a co-chaperone of the GR that impairs efficient nuclear translocation of the GR. The Fkbp5 gene is a target of GR-mediated transcription, resulting in negative feedback on GR nuclear translocation. While interactions of FKBP5 with GR have been previously shown in cell models, we investigate here whether prior exposure to CAS and acute stress interact to alter interactions between the GR and FKBP5 in the adult rat hippocampus. In order to assess the adult consequences of CAS in the rat brain and the potential of prior exposure to CAS to alter the adult GR response to acute stress, the current study assessed the extent to which CAS impacts adult GR localization and regulation at baseline and following exposure to an acute novel stressor in adulthood in both male and female rats.

Methods: Male and female Wistar rats were exposed to a mixed-modality CAS paradigm consisting of isolation, restraint, and social defeat during mid-adolescence (PND 38-49). Adult rats (PND 94) were exposed to an acute novel forced swim stressor (5-minutes) and tissue was collected 15, 30, or 120 minutes following stressor exposure. A separate group of male and female rats was collected at baseline without adult exposure to a stressor. Rats were euthanized via rapid decapitation, and brains were frozen on dry ice and stored at -80 °C prior to processing. Hippocampal hemispheres were dissected or sectioned for analysis. Nuclear and cytosolic protein fractionation and western blot were used to assess nuclear GR protein in the hippocampus. Densitometry units for GR protein expression were normalized to H3 loading control protein ($n = 8$-10/group). Quantitative reverse-transcription polymerase chain reaction (PCR) was used to assess gene expression of Fkbp5 in the hippocampus. ΔCt values were used for statistical analysis ($n = 9$-11/group). A separate group of brains was cryosectioned at 7 µm thickness, and a proximity ligation assay (PLA) was used to assess interactions between the GR and FKBP5 in situ in the hippocampus. Number of PLA interactions were normalized to negative technical controls ($n = 6$/group). Two-way ANOVA (CAS x acute stress) was used to assess statistical significance of results ($\alpha = 0.05$).

Results: A history of CAS and novel acute stressor exposure interacted in adult females ($F(3, 70) = 2.96$, $p = 0.04$), but not males ($F(3, 63) = 0.744$, $p > 0.05$), to impact nuclear localization of GR protein. Specifically, CAS reduced nuclear localization of the GR 30-minutes following exposure to an acute novel stressor in adult females (Sidak's multiple comparisons test, $p = 0.029$), suggesting impaired translocation. CAS alone did not impact nuclear GR in males ($F(1, 63) = 0.22$, $p > 0.05$) or females ($F(1, 70) = 0.57$, $p > 0.05$). CAS elevated basal gene expression of Fkbp5 in females ($t17 = 2.22$, $p = 0.04$). Furthermore, a history of CAS exposure interacted with a novel stressor challenge in adulthood to increase GR-FKBP5 interactions in the dorsal CA1 region of the hippocampus in adult females ($F(1, 20) = 6.11$, $p = 0.02$), but not males ($F(1, 20) = 0.15$, $p > 0.05$), and specifically, adult female rats with a history of CAS exposure exhibited increased interactions of GR and FKBP5 following an acute novel stressor exposure ($p = 0.02$, Tukey's multiple comparisons test). There was no significant impact of CAS on GR-FKBP5 interactions in the CA1 in males ($F(1, 20) = 1.29$, $p > 0.05$).

Conclusions: These studies establish that localization and regulation of the hippocampal GR is susceptible to long-term dysregulation following adolescent stress exposure in a sex-specific manner. In adult females, prior exposure to stressors during adolescence impairs GR nuclear localization in response to an acute novel stressor. Furthermore, CAS increases basal Fkbp5 expression and increases interactions of the GR with FKBP5 proteins following a subsequent acute stressor exposure in adulthood. These studies show that there are long-term effects of CAS on FKBP5's interactions with the GR that are sex-specific. Collectively, these studies suggest increased negative feedback on GR localization in the adult female hippocampus through increased interactions between GR and FKBP5. These studies identify FKBP5 and its interactions with the GR as a sex-specific consequence of CAS exposure that is revealed following adult stressor challenge and suggest that FKBP5's actions on the GR could be a potential target for sex-specific interventions for stress-related disorders.

Keywords: Acute and Chronic Stress, Glucocorticoid Dysregulation, FKBP5, Sex Differences, Early Life Stress

Disclosure: Nothing to disclose.

W31. Minocycline Augmentation of Serotonin Reuptake Inhibitors in Pediatric OCD: Randomized Control Trial to Test Feasibility, Acceptability, Efficacy, and Striatal Glutamate Effects

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Background: Obsessive-compulsive disorder (OCD) is a disabling illness that often begins in childhood or adolescence. The only medications approved by the Food and Drug Administration (FDA) are serotonin reuptake inhibitors (SRIs), which typically lead to a 20-40% reduction in symptoms, and the only proven SRI augmentation strategy in pediatric OCD is cognitive-behavioral therapy (CBT). There are no controlled trials to support augmentation medication strategies in children. Drugs that modulate the brain glutamate system may provide new hope for pediatric OCD. Minocycline, approved by the Food and Drug Administration in youth, crosses the blood brain barrier and is thought to have neuroprotective effects by increasing the uptake of glutamate (Glu) by glial cells and inhibiting microglial proliferation. Thus, to evaluate the acceptability, tolerability, and preliminary efficacy of adding minocycline to SRIs we conducted a randomized placebo-controlled trial in youth (ages 8 to 20) with

OCD; and we also tested minocycline's mechanism of action by measuring glutamate (Glu) in the caudate using magnetic resonance spectroscopy (MRS) both at baseline and after treatment.

Methods: Participants had a principal diagnosis of OCD (≥ 1 year) and OCD symptoms of at least moderate severity (Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS] score ≥ 16). All were receiving a serotonin reuptake inhibitor (SRI) at an adequate and stable dose (≥ 12 weeks) and reported at least a minimal SRI response. Other anxiety diagnoses were permitted with OCD as primary. Major psychiatric and medical disorder diagnoses were excluded as well as a body weight less than 30.0 kg, presence of metal in the body, pregnant/nursing, or receiving cognitive behavioral therapy. After providing informed assent/consent, participants were randomized (2:1) to receive minocycline (max weight-based dose of 200 mg per day) versus placebo in addition to their stable SRI dose for 12 weeks. Clinical and safety assessments were performed by independent evaluators at baseline and every 4 weeks. MRS was conducted on a General Electric 3.0 T MR system. Structural MRI consisted of a series of standardized axial, coronal and sagittal T1-, T2-, and spin density-weighted scans, with slices appropriately obliqued for prescribing the 1 H MRS voxels. Levels of glutamate (Glu) obtained with the constant-time PRESS (CT-PRESS) MRS technique. Baseline characteristics were compared between groups using two-sample t-test for continuous variables and chi-squared tests for categorical variables. Linear mixed effects models with subject-specific random intercepts and covariates (race and history of CBT) were fitted to the CY-BOCS, the primary clinical outcome, and to brain measures of Glu in the left caudate.

Results: Of the 215 participants phone screened, 38 were eligible and 31 were randomized to either the addition of minocycline ($n = 21$), or placebo ($n = 10$), and 26 of the subjects completed at least 10 weeks of acute treatment. Dropout did not significantly differ by treatment group (minocycline: 4 of 21; pill placebo: 1 of 10; Fisher exact test, $p = 1.000$). Those randomized to minocycline versus placebo were well-matched on all demographic and clinical factors except those receiving minocycline were more likely to be white ($p < 0.05$). Using mixed effects models, the decrease in OCD severity over time (via the CY-BOCS) was greater in minocycline than in placebo but did not reach statistical significance (between group change: mean [SE], -2.03 [1.40]; 95% CI, -4.81to 0.75, $p = 0.15$; ES = -0.57). Both groups showed a small within-group mean decrease in CY-BOCS (minocycline: -3.31[0.82]; placebo: -1.27 [1.13]), with only the change in the minocycline group reaching significance ($p < 0.001$). There were no significant between-group differences in change in Glu (mean [SE], -02.93 [1.99]; 95% CI [-7.13, 1.28]; $p = 0.16$; ES = -0.35). Both groups had a mean decrease in Glu (minocycline: -3.90[1.11]; placebo: -0.97 [1.65]) with only the minocycline group's decrease being significant ($p = 0.003$). However, the change in Glu did not correlate with the change in CY-BOCS. There were 5 serious adverse events.

Conclusions: 1) Feasibility: Many pediatric OCD subjects had not previously received an adequate SRI trial and thus were not yet eligible for this study. 2) Acceptability: Many pediatric OCD subjects and their families were interested in alternatives to SRIs and CBT. Most tolerated minocycline augmentation however several participants experienced a serious adverse event.

3) Efficacy: Minocycline augmentation had a modest overall effect although in a refractory OCD clinical pediatric sample. 4) Striatal glutamate effects: Minocycline had modest effects on striatal glutamate levels but change in striatal glutamate levels did not correlate with change in OCD symptoms in this sample.

Keywords: Children and Adolescents, Obsessive Compulsive Disorder, Magnetic Resonance Imaging, Clinical trial, minocycline

Disclosure: Neurocrine Biosciences, Inc, Grant, UpToDate, Royalties, Oxford Press, Honoraria, New York State OMH, Honoraria

W32. Transdermal Cannabidiol (CBD) Gel for the Treatment of Fragile X Syndrome (FXS)

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Background: FXS is a genetic condition caused by a mutation in the Fragile X mental retardation 1 (FMR1) gene located on the X chromosome (De Boulle et al. 1993). Mutations in the FMR1 gene silence the expression of the Fragile X mental retardation protein (FMRP), an essential protein for normal synaptic function, synaptic plasticity, and the development of neuronal connections during brain maturation. The absence of FMRP in neurons accounts for many of the neuropsychiatric symptoms of Fragile X.

Dysregulation of the endocannabinoid pathways in the central nervous system is thought to contribute to clinical abnormalities seen in FXS. CBD may attenuate the loss of endogenous endocannabinoid signaling in FXS, bypassing the FMRP deficiency. Beyond its potential to re-regulate the endocannabinoid system of patients with FXS, numerous studies have demonstrated the anxiolytic effects of CBD via its impact on 5-HT1A (serotonin).

Anxiety and social avoidance are core features of FXS (Cordeiro et al., 2011; Sansone et al., 2012; Scherr et al., 2017). Social avoidance has been defined as a behavioral response to anxiety that arises from social interaction; thus, anxiety can be thought of as foundational precipitant to social avoidance. Social avoidance encompasses behaviors such as social isolation, social escape behaviors and gaze avoidance that distance the individual from his/her social counterparts. Parent/caregiver feedback suggests the most challenging symptoms to manage in FXS are anxiety, difficulties related to social interaction, avoidance and isolation, and aggressive behavior (Hessl and Zynerba Data on File). Parents/caregivers describe problematic behaviors as meltdowns, inattention, awkwardness and avoidance. While parents/caregivers describe their children as wanting to be in social situations, their anxiety does not allow them to do so.

Methods: This open-label study evaluated the safety, tolerability and initial efficacy of ZYN002 (transdermal CBD gel) for the treatment of childhood/adolescent FXS behavioral and emotional symptoms. During the first 6 weeks, patients were titrated from an initial daily dose of CBD 50 mg up to a maximum of 250 mg CBD daily. Patients were maintained on a maximum of 250 mg CBD daily for the remaining 6 weeks of the study (Maintenance Period). Two key endpoints include the Anxiety, Depression, and Mood Scale (ADAMS) and Aberrant Behavior Checklist (ABC-CFXS). Following the 12-week open-label study, patients were allowed to roll into a 2-year open-label extension study.

Results: Twenty patients (mean age = 10.4, SD = 3.9) were enrolled for the 12-week treatment period. Significant gains from baseline were observed across all outcome measures. Average improvement over baseline in overall anxiety and depression (ADAMS Total Score) reached 46% ($p < 0.0001$), with particular benefit observed for the General Anxiety (54%; $p < 0.0001$), Social Avoidance (53%; $p = 0.0002$), and Compulsive Behavior subscales (50%; $p = 0.0262$). Additionally, improvements as high as 59% (Stereotypy subscale; $p = 0.0006$) were observed for aberrant behavior (as measured by ABC-CFXS), with Social Avoidance (55%; $p = 0.0005$), Social Unresponsiveness/Lethargy subscales (53%; $p = 0.0034$) and Irritability (42%; $p = 0.0096$) each also improving dramatically during the treatment period.

Thirteen (72%) of the 18 patients who completed the initial 12-week study rolled into the open-label extension. One patient has discontinued for administrative reasons. While the open-label study is ongoing, data through Week 51 (12 weeks in initial study and up to 9 months in the extension study) is being reported.

Results from the extension study demonstrate continued gains in two measures collected (ADAMS and ABC-CFXS). Patients who have completed a Week 51 visit reported significant gains from baseline in ADAMs total score, with participants experiencing an average improvement of 54%; $p < 0.0001$. Similar improvement from baseline was observed for aberrant behavior, ranging from 77%; $p = 0.0013$ (Social Avoidance subscale) to 59%; $p = 0.0007$ (Irritability subscale) and 72%; $p = 0.0035$ (Socially Unresponsiveness/Lethargy subscale) at Week 51.

ZYN002 was well tolerated. No serious adverse events are reported and no clinically meaningful trends in vital signs, electrocardiogram or clinical safety labs, including liver function tests. The most common treatment-emergent adverse events are mild-moderate gastroenteritis and upper respiratory infections, both presumed to be unrelated to study drug.

Conclusions: These open-label findings highlight both the short- and long-term positive impact of ZYN002 on emotional and behavioral symptoms experienced by children and adolescents with FXS. A randomized, double blind, placebo-controlled trial to extend these findings to a larger population of children and adolescents with FXS has been initiated.

Keywords: Fragile X Syndrome, Cannabidiol, Social Anxiety, Social Functioning

Disclosure: Zynerba, Advisory Board, Astellas, Advisory Board

W33. Repetitive Transcranial Magnetic Stimulation for the Treatment of Executive Function Deficits in Autism Spectrum Disorder

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Background: Executive function (EF) deficits in patients with autism spectrum disorder (ASD) are ubiquitous and understudied. There are no effective, neuroscience-based treatments to address this impairing feature of ASD. Repetitive transcranial magnetic stimulation(rTMS) has demonstrated promise in improving EF deficits in adult neuropsychiatric disorders. Here, we present results for the first double-blind, randomized-controlled trial of bilateral, 20 Hz, rTMS applied to dorsolateral prefrontal cortex (DLPFC) for treatment of EF deficits in ASD. The objectives of this pilot study were to examine the feasibility of implementing our rTMS protocol and evaluate the effects of rTMS on spatial working memory (SWM) performance in youth and emerging adults with ASD.

Methods: Forty youth and emerging adults, aged 16-35, with confirmed ASD without intellectual disability and with impairment in everyday executive function skills based on subscale impairment on the Behavior Rating Inventory of Executive Function (BRIEF)-Adult, participated. Participants were tested using the Cambridge Neuropsychological Test Automated Battery (CANTAB) SWM task before and after rTMS and at one-month follow-up. Secondary outcome measures included the BRIEF meta-cognition index and 0- and 2-back SWM tasks. Neuronavigation-guided rTMS stimulating bilateral DLPFC sequentially (750 pulses/side at 20 Hz) for 20 treatments was used. Mixed-effects models including treatment, time and treatment by time interaction as predictors of interest were used to examine effects of rTMS ($n = 20$, $23.5 y \pm 4.2$,14 M) versus sham ($n = 20$, $21.65 y \pm 4.6$, 14 M) treatment on primary and secondary outcome measures.

Results: Two participants from the active group dropped out due to challenges travelling for daily participation. 38/40 participants completed the full rTMS treatment protocol (34 completed one month follow up). Rate of adverse effects did not differ between active and sham groups. A significant main effect of time ($F2,67 = 5.2$, $p = 0.008$), but no effect of treatment group x time was found for CANTAB SWM total errors as well as BRIEF MCI scores, indicating that these measures were susceptible to practice effects. In contrast, rTMS significantly decreased the number of missed items on the 2-back SWM task compared to sham ($F1,28 = 4.20$, $p = 0.049$). In addition, post-hoc analysis indicated a significant three-way interaction between treatment group, time and adaptive functioning for CANTAB SWM performance ($F2,64 = 3.15$, $p = 0.049$), where SWM total errors significantly decreased in ASD participants with lower adaptive functioning who received active rTMS but not sham treatment.

Conclusions: Our pilot study indicates that 20 Hz rTMS to DLPFC was well tolerated in youth and emerging adults with ASD. Although the CANTAB SWM and BRIEF MCI scores were susceptible to practice effects in the current sample, improvement in performance of the 2-back SWM task was found with active rTMS compared to sham. Further, adaptive functioning moderated the effect of active treatment on SWM performance in ASD. These pilot data suggest that bilateral rTMS for EF deficits in ASD is safe, well tolerated and may be efficacious for treatment of SWM deficits. Further study with larger samples and potentially focused on individuals with ASD with lower adaptive functioning is warranted.

Keywords: Neurostimulation, Autism Spectrum Disorder, Treatment, Executive Function

Disclosure: Nothing to disclose.

W34. Developmental Maturation of Inhibitory Control Circuitry: A Large-Scale Longitudinal fMRI Study

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Background: Inhibitory control involves the ability to voluntarily suppress goal- or task-irrelevant information. Improvement in this cognitive process from childhood to adulthood is widely attributed to maturation of the neural networks that supports inhibitory control, including the anterior cingulate cortex, prefrontal cortex (including the inferior frontal gyrus and the dorsal lateral prefrontal cortex), posterior parietal cortex, striatum, and cerebellum. Functional magnetic resonance imaging (fMRI) studies investigating age-related differences across development have reported both activation decreases and increases in areas that are key for inhibitory control, such as the prefrontal cortex. One potential reason for this inconsistency is the variable developmental periods during which participants were scanned. Since substantial and diverse developmental changes occur in response inhibition circuitry across adolescence and into young adulthood, any gaps between measurement groups (e.g., comparing 12–16-year-olds with 18–21 year-olds) or limiting the age range of participants (e.g., 13–17 years, which eliminates earlier and later developmental time periods) can present an incomplete picture. Therefore, the purpose of this analysis was to characterize the maturation of inhibitory control brain functionality over a wide developmental age range in a large sample of youth at risk for alcohol and other substance use disorders.

Methods: Participants were 290 individuals (62% male) who were part of the larger Michigan Longitudinal Study, a prospective study of families with high levels of parental alcohol use disorder (AUD) and a contrast sample of non-AUD families. Participants were scanned with fMRI on a go/no-go task approximately every 1–2 years. There were a total of 1162 scans, with each participant

contributing 1–8 scans. The overall mean scan age was 18.9 (SD 5.2), with a minimum age of 7.6 and a maximum age of 28.5. The Sandwich Estimator Toolbox for Longitudinal and Repeated Measures Data was used to characterize age-related changes in hemodynamic response associated with successful inhibitory control. The contrast of interest was correct rejections vs. implicit baseline. As recommended, age was partitioned into between-subject and within-subject variance so as to account for practice effects. Task performance (i.e., correct rejection rate) was also included in the model to account for age-related performance improvements. In addition to the full sample, models for males (720 scans) and females (422 scans) were run separately to characterize sex differences in the effects. All results were thresholded at a false discovery rate of $p < .05$ to correct for multiple comparisons.

Results: In the full sample, the mean correct rejection rate was 68.2% (SD 19.3%), and correct rejection rate was significantly correlated with age, $r = .43$, $p < .001$. Females also had a higher correct rejection rate than did males, $t(1019) = 4.86$, $p < .001$. In the full sample, there were between-subject age-related activation increases during successful inhibitory control in prefrontal and subcortical areas, including the superior frontal gyrus (Brodmann areas [BA] 8 and 10), amygdala, and putamen. In the male-only subsample, there were similar areas of age-related activation increases, with the addition of the globus pallidus, temporal areas including the superior temporal gyrus (BA 38), and prefrontal areas including the middle frontal gyrus (BA 9) and inferior frontal gyrus (BAs 11 and 47). In the female-only subsample, there were no significant age-related activation increases. In addition, there were no age-related decreases in activation for any of the models.

Conclusions: This study utilized a large sample of at-risk youth (1162 scans over 21 years of development) to characterize age-related changes in inhibitory control circuitry. A number of significant regions were found in both the full sample and the male-only sample, including traditional inhibitory control areas in the prefrontal cortex. In addition, we found regions not commonly identified in go/no-go studies, including the amygdala and temporal areas. In contrast, there were no significant results for the female-only sample at the chosen threshold, due possibly to the smaller sample size relative to the full and male-only samples. This study is valuable because much of what we know about the maturation of inhibitory control functioning comes from cross-sectional or age-limited analyses, thus obscuring the true nature of the effects.

Keywords: Response Inhibition, Functional MRI (fMRI), Longitudinal Imaging, Children and Adolescents, Young Adults

Disclosure: Nothing to disclose.

W35. Transcriptional Priming by Enduring Chromatin Modifications After Early Life Stress

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Background: Child maltreatment and other forms of early life stress increase the lifetime risk of depression and other mood, anxiety, and drug disorders by 2-4 -fold. Studies in humans and animals suggest that early life stress sensitizes individuals to stress later in life, leading to a first appearance or synergistic worsening of depression-like symptoms only after additional stress. To study the molecular correlates of lifelong stress vulnerability, we recently established a "two-hit" stress paradigm in mice in which early life stress in a sensitive window increases susceptibility for depression-like behavior, but only after experience of an additional stressor in adulthood. This latent behavioral vulnerability is accompanied by latent transcriptional alterations in key brain reward regions that are implicated in depression, including the ventral tegmental area (VTA; Peña et al., Science, 2017). We hypothesized that such latent transcriptional alterations would be primed by post-translational histone modifications.

Methods: In order to profile all possible long-lasting histone modification changes, we performed bottom-up mass spectrometry on isolated histone tail fragments from VTA of adult standard-reared and early life stressed adult male mice. We also performed ChIP-seq for monomethylated histone H3 lysine 4 (H3K4me1) from the same groups. Finally, we compared differentially enriched H3K4me1 genomic regions to our previous RNA-seq data and to 3-dimensional Hi-C chromatin conformation data from mouse brain to assess regions of potential enhancer contact.

Results: The proportions of 14 histone H3 and H4 modifications were altered by early life stress, a majority of which are associated with permissive gene expression states. Among these, early life stress increased H3K4me3 and H3K4me1, marks of active and primed cis-regulatory elements. ChIP-seq for H3K4me1 revealed 209 differentially enriched peaks (FDR < 0.05 and > 20% fold-change), a majority of which were increased by early life stress. Interestingly, there is greater correspondence between H3K4me1 enrichment and expression of nearest-genes after additional adult stress than after early life stress alone.

Conclusions: Enduring changes in histone modifications suggest early life stress promotes a more open/permissive chromatin state in the VTA. H3K4me1 ChIP-seq analysis in the context of our RNA-seq and HiC data suggest that this mark may participate in priming gene expression changes to a second stress in adulthood. This research suggests novel epigenetic mechanisms mediating the long-lasting effects of early life stress within brain reward circuitry.

Keywords: Early Life Stress, Epigenetic, ChIP-Sequencing, Ventral Tegmental Area (VTA)

Disclosure: Nothing to disclose.

W36. 22q11.2 CNV: Tbx1 is Required for Proliferation of Neonatal Neural Progenitor and Social Cognition

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Background: Copy number variants (CNVs) at 22q11.2, ranging from 1.5 Mb to 3.0 Mb, are associated with schizophrenia, autism spectrum disorder (ASD), intellectual disorder (ID) and major depressive disorder. However, how individual 22q11.2-encoded genes contribute to dimensional aspects of many mental illnesses is still poorly understood. My group and others have systematically examined the contribution of small segments of 22q11.2 in mouse models and narrowed down specific chromosomal segments that contribute to distinct behavioral dimensions. The transcription factor Tbx1 is one of four genes encoded in a 200 kb segment that functionally contributes to repetitive behaviors and social interaction deficits. We have further tested the cellular and molecular substrates through which Tbx1 deficiency causes behavioral dimensions relevant to neuropsychiatric disorders.

Methods: Male nestinCreERT;Tbx1flox/+ mice were treated with Tamoxifen at postnatal days 1 to 5 (P1-5) or postnatal days 21 to 25 (P21-25) and tested for reciprocal social interaction and other behaviours 1 month later (n = 9-22 mice/group). Hippocampal progenitor cells derived from P0 neonatal pups were passaged and cultured to evaluate expression of Tbx1 during cell

cycle (n = 4-6 culture dishes/group) and the role of Tbx1 in the proliferation of progenitor cells (n = 4-5 culture dishes/group). The target genes of Tbx1 were screened by ChIP-seq and validated by ChIP, Tbx1 knockdown and deletion and mutation of the promoter region of a target gene (n = 6-27 culture dishes/group).

Results: Induction of Tbx1 heterozygosity in neural progenitor cells reduced reciprocal social interaction more effectively when it was initiated at P1-5 than at P21-25 ($P < 0.05$). Tbx1 expression peaked shortly before cell proliferation in vitro ($P < 0.05$). Knockdown of Tbx1 reduced the rate of proliferation of neural progenitor cells in vitro ($P < 0.05$). ChIp-seq identified peaks within 1000 bp of which 196 known genes are located in vitro, one of which was Pten. This was validated by ChIP. Tbx1 was found to be expressed in Pten-positive cells in the hippocampal granule cell layer in vivo. Knockdown of Tbx1 by siRNA reduced the transcription and expression of Pten in vitro ($P < 0.05$). Segmental deletions and point mutations of the Pten promoter significantly reduced its transcriptional efficacy, as revealed by luciferase assays ($P < 0.05$).

Conclusions: Tbx1 deficiency in progenitor cells during the neonatal period impairs social cognition and motivation through its impact on the proliferation of progenitor cells. Pten was identified as one of the target genes of Tbx1. A molecular cascade from Tbx1 to Pten and its downstream molecules could be targeted for therapeutic options for defective social cognition and motivation in many 22q11.2 CNV-associated psychiatric disorders.

Keywords: Copy Number Variant, ASD, Schizophrenia, Stem Cells, Neural Progenitor Cells

Disclosure: Nothing to disclose.

W37. Polygenic Expression Score Reveals Impact of DCC and its Network on Brain Morphology and Behavior of Healthy Children

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Background: The guidance cue receptor DCC determines the organization of pre- and postsynaptic components of prefrontal cortex dopamine circuitry, markedly influencing functional and behavioral outputs. Studies in mice reveal that variations in DCC expression lead to changes in cognitive flexibility, behavioral inhibition, vulnerability to stress induced depression-like behaviors, and are induced by exposure to drugs of abuse. In parallel, an increasing number of genomic meta-analysis and post-mortem human studies show a strong genetic correlation between DCC and psychiatric conditions, most notably major depressive disorder. Together this evidence supports the notion that DCC receptors, by controlling the maturation of the prefrontal cortex, contribute to the development of susceptibility to (and/or resilience against) psychopathologies. Indeed, in a recent study we show that healthy adults with an autosomal dominant DCC mutation have alterations in the structural and functional connectivity of mesocortical pathways and in related behavioral traits (Vosberg et al. 2018). To further these studies, we created a polygenic expression score to assess whether variations of DCC co-expressed genes in the prefrontal cortex are involved in healthy human development. We used genetic, neuroimaging, and behavioral data from a child cohort. We tested the hypothesis that discrete differences in behavior and brain structure will emerge according to child's genotype expression. Our goal is to eventually be able to identify susceptible individuals early in life.

Methods: This study utilizes a network of genes that are co-expressed with DCC in the prefrontal cortex during young age, as they represent coherent gene networks. We created the polygenic expression score by obtaining single nucleotide polymorphisms (SNPs) in highly co-expressed genes in the PFC in postmortem donors between the ages of 1.5 to 11 (databases: Brainspan and braineac). Then, using GTEx regression model of gene expression, we extracted the slope coefficient as the weight for alleles. The polygenic expression score is created by combining the estimated effects of alleles for the SNPs that each subject carries. We used the polygenic expression score to investigate how the DCC network can uncover developmental differences in a cohort of Canadian children (MAVAN project). Followed from birth to 12 years of age with multiple behavioral measures (n = 260; 131 females), 64 of the healthy volunteers (n = 64; 33 females) underwent magnetic resonance imaging (MRI) and had genetic data collected using genotype sequencing (Psychip/Psycharray).

Results: Here we present new evidence on the impact of DCC and its gene co-expression network on brain development and behavior in a healthy population. Specifically, children with high polygenic score have significantly smaller brain volumes ($p = 0.016$, $F = 6.22$), when adjusted for age, sex and ethnicity. Volumetric thalamus measures are smaller in children with high co-expression scores ($p = 0.032$, $F = 4.86$) and are especially evident in boys ($p = 0.030$, $F = 4.99$). Measures of behavioral impulse control, using the CANTAB Stop Signal test, reveal that high polygenic score group exhibits lower response inhibition ($p = 0.034$, $F = 4.55$).

Conclusions: Genetic variations in DCC associate with differential vulnerability to psychopathologies involving prefrontal cortex dysfunction. Our present findings indicate that high or low expression of the prefrontal cortex DCC co-expression network predicts individual differences in brain morphology that are apparent at an early age in a healthy population. We now plan to test our findings in a larger and ethnically diverse population, and to assess the possible contribution of alterations in connectivity using diffusion tensor imaging.

Keywords: Guidance Cues, Bioinformatics, Genetic Score

Disclosure: Nothing to disclose.

W38. Neural Markers of Eye Gaze to Face Emotion in Pediatric Irritability

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Background: Irritability, an increased proneness to anger relative to one's peers, is a common and impairing clinical phenotype in youth (reviewed in Brotman et al., 2017). Of the limited pathophysiological research on pediatric irritability to date, one of the most replicated findings is a broad deficit in identifying or labeling facial emotional expressions (Guyer et al., 2007; Kim et al., 2013; Rich et al., 2008). Functional neuroimaging methods may help to elucidate brain-behavior mechanisms of face emotion labeling deficits in irritability. One previous fMRI study found that dimensional levels of irritability in youth with disruptive mood dysregulation disorder (DMDD) were associated with alterations in neural activation during face emotion labeling (Wiggins et al., 2016). Here, we integrated fMRI and eye-tracking methods to interrogate how transdiagnostic, dimensionally-assessed irritability relates to neural markers of eye gaze during face emotion labeling.

Methods: fMRI data were acquired from 65 youth varying in level of irritability (mean age = 14.7 years; 42% female; n = 21 with disruptive mood dysregulation disorder, n = 24 with attention-deficit/hyperactivity disorder, and n = 20 healthy volunteers). Irritability was assessed using the Affective Reactivity Index (ARI)

parent- and youth-report (Stringaris et al., 2012). We employed confirmatory factor analysis in which ARI item scores served as indicators of an overarching irritability latent factor; this statistical model fit the data well (CFI = .989; NNFI = .987). Participants' scores on the irritability latent factor were extracted for use in fMRI analysis. A canonical face-emotion labeling paradigm assessed youth's neural activity as a function of stimulus face emotion (angry, fearful, happy) and intensity of expression (0% [neutral], 50%, 75%, 100%). Following fMRI, participants completed an identical eye-tracking paradigm that assessed gaze (duration, fixations) to the faces' eye regions as salient emotion cues (Kim et al., 2013). Whole-brain linear mixed effects analyses in AFNI examined neural activity during face emotion labeling in relation to youth's level of irritability and gaze fixation behavior (voxelwise threshold $p < .005$; whole-brain multiple-testing correction to $\alpha = .05$; $k > 73$ [1141 mm3]). In-scanner motion was a covariate.

Results: Higher irritability was associated with fewer gaze fixations to faces' eye regions for specific face intensities relative to others (75% vs. 50%, $p = .03$; 75% vs. 100%, $p = .02$). With respect to neural activation, irritability, face intensity, and gaze fixation behavior interacted in relation to widespread activation in the orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, insula, and several other regions (all $ps < .005$, whole-brain corrected). While specific interactive effects varied by brain region, in general, youth with higher vs. lower levels of irritability showed opposing patterns in how their eye gaze related to brain function in these regions. In addition, irritability, face emotion, and gaze fixation behavior interacted in relation to activation in the temporal pole and precentral gyrus (all $ps < .005$, whole-brain corrected). Last, irritability, face emotion, and face intensity interacted in relation to ventromedial prefrontal cortex (vmPFC) activation ($p < .005$, whole-brain corrected). Specifically, higher irritability was associated with decreased vmPFC activation when labeling moderate-intensity angry faces relative to both high-intensity angry faces and moderate-intensity fearful faces.

Conclusions: Transdiagnostic, dimensionally-assessed irritability was associated with widespread neural dysfunction during face emotion labeling. Specifically, youth's levels of irritability interacted with their patterns of visual attention on the task in relation to brain function. This suggests that the neural substrates of visual attention to faces' salient emotion cues vary by level of irritability. In addition, irritability was associated with decreased vmPFC activation when labeling moderate-intensity (i.e., ambiguous) angry faces relative to other face emotion types. Given that the vmPFC is normatively activated during emotion labeling, serving a regulatory function over limbic regions (Lieberman et al., 2007), this pattern in irritable youth may be associated with emotion dysregulation. Thus, a potential target for neurobehavioral intervention may be to increase vmPFC activation as irritable youth label these faces and to assess associations with emotion regulation. Further research on the brain-behavior mechanisms of face emotion labeling deficits in irritability may help guide the development of novel, targeted interventions.

Keywords: Functional MRI (fMRI), Children and Adolescents, Irritability, Eye-Tracking

Disclosure: Nothing to disclose.

W39. Hippocampal Subfield Volumes Reduced by Binge Drinking of Alcohol in Adolescents

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Background: Alcohol use during adolescence has been associated with higher rates of binge drinking, increased risky behavior, and impulsivity. This crucial period of development makes adolescent brains even more vulnerable to the deleterious impact of binge drinking. Longitudinal studies have illustrated the abnormal growth patterns and overall accelerated gray matter loss following heavy alcohol use (Squeglia et al., 2014, Spear, 2018). There have been inconsistent results from cross-sectional reports examining the effects of alcohol use on whole hippocampal volume (De Bellis et al., 2000, Nagel et al., 2005, Hanson et al., 2010). However, a recent meta-analysis found problematic alcohol use to be associated with significantly smaller hippocampal volume (Wilson et al., 2017). This effect was stronger in adults than adolescents, but longitudinal insight is needed. The hippocampus is a region of particular interest because of its role in memory, learning, and emotional processes. Moreover, animal models suggest that the hippocampus may be especially vulnerable to environmental stressors (Kim & Diamond, 2002). The present study sought evidence for altered adolescent hippocampal subfield volumes associated with binge drinking in a national, prospective study of adolescents before and after initiation of alcohol use.

Methods: Subjects were recruited at the Duke research site for the National Consortium on Alcohol & Neurodevelopment in Adolescence (NCANDA) study and included 175 adolescents (84 females and 91 males) ages 12 to 21. Each subject completed clinical and neuroimaging assessments at baseline and annual follow-ups at years 1 ($n = 148$), 2 ($n = 127$), 3 ($n = 105$), and 4 ($n = 51$). High resolution T1-weighted anatomical scans were acquired on a 3 T GE MR750 scanner. The Customary Drinking and Drug Use Record (CDDR) was used to assess binge drinking behavior at each of the 606 total study visits. Image preprocessing and longitudinal segmentation of hippocampal subfields were completed using FreeSurfer, segmenting 12 bilateral regions. We used R and lme4 (Bates, Maechler & Bolker, 2012) to perform a linear mixed effects analysis of the relationship between hippocampal subfield volumes and binge drinking behavior. The fixed effect used to create the model was binge drinking. Random effects included intercepts for age, intracranial volume, as well as by-subject random slopes for the effect of binge drinking. Likelihood ratio tests of the full model with the effect of binge drinking were tested against a null model in an ANOVA.

Results: Of the 606 individual study visits, 79 of these met binge drinking criteria for the subject's age and gender, 140 met moderate drinking criteria, while 387 endorsed no appreciable history of alcohol use. Linear mixed effects models revealed decreased hippocampal subfield volume associated with binge drinking in the left whole hippocampus ($\chi2\ (1) = 5.70$, $p = 0.016$), left subiculum ($\chi2\ (1) = 4.69$, $p = 0.030$), and left presubiculum ($\chi2\ (1) = 5.81$, $p = 0.015$). Right hippocampal subfield volumes were not significantly associated with binge drinking behavior.

Conclusions: The left subiculum and left presubiculum in particular, may play an important role in adolescent alcohol use. Our results provide initial evidence that binge drinking leads to a decrease in subiculum and presubiculum volumes in adolescents and confirm reports from cross-sectional analyses of adults with alcohol dependence.

Keywords: Longitudinal Imaging, Adolescent Alcohol Use, Hippocampal Subfields

Disclosure: Nothing to disclose.

W40. Childhood Maltreatment and Psychopathology Show Unique Brain Structural Correlates in Adolescent Girls

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Background: Recent meta-analyses of childhood maltreatment (Lim et al, 2014) and psychopathology (Goodkind et al, 2015) are associated with gray matter volume (GMV) reductions in potentially common regions including the prefrontal cortex, insula, and hippocampus. However, given the frequent co-occurrence of maltreatment history and psychopathology, further study is needed to determine whether maltreatment and psychopathology are characterized by unique and/or interactive effects on GMV. Here we report results from a large-scale investigation of brain morphometry in adolescent girls with varying levels of childhood maltreatment and psychopathology.

Methods: A pooled cohort of 169 females between the ages of 8-18 (ave. 14.7 yrs) were recruited by 5 independent studies investigating interpersonal violence-related psychopathology (predominantly PTSD). Each girl completed assessments for psychopathology, childhood maltreatment history (CTQ), and underwent high resolution, T1 structural magnetic resonance imaging (MRI). We used whole-brain voxel-based morphometry (VBM) within a general linear model to characterize unique effects of maltreatment and presence of psychopathology ($n = 71$ with and $n = 98$ without), and the interaction of CTQ and psychopathology status. Analyses were covaried for age and intracranial volume and subject to whole brain correction (threshold $k = 266$ voxels). In conjunction, we implemented a random forest feature learning algorithm on whole brain parcellated VBM volumes to determine the most relevant GMV biomarkers in predicting maltreatment exposure and psychopathology.

Results: In the general linear model, psychopathology status was associated with reduced GMV in multiple prefrontal regions including ventromedial, ventrolateral, and dorsolateral prefrontal cortex (PFC). CTQ scores were inversely associated with GMV in additional regions including dorsomedial PFC and insula. Furthermore, we identified a psychopathology by CTQ interaction in the bilateral hippocampus. In youth without psychopathology, CTQ was inversely associated with hippocampal GMV. In contrast, youth with psychopathology showed a positive relationship between CTQ and hippocampal GMV, a relationship that was driven primarily by girls with SSRI exposure. In the random forest analysis, feature sets including the ventrolateral and dorsolateral, cingulate cortex, and hippocampus led to successful prediction of maltreatment exposure and psychopathology significantly better than chance (accuracy 65%).

Conclusions: These results suggest potentially unique gray matter substrates of psychopathology and maltreatment exposure in an adolescent female population. Such patterns may be informative for identifying neural substrates of vulnerability and resilience to childhood maltreatment and may indicate a biological signature for maltreatment as a unique subtype of mental illness. Furthermore, these findings warrant assessment of SSRI and other psychiatric medication exposure in studies of maltreatment and psychopathology, given the unexpected relationship of CTQ to hippocampal volume in adolescent girls with psychopathology. Future studies will be needed to test these relationships in males and broader types of psychopathology.

Keywords: Childhood Maltreatment, Pediatric PTSD, Machine Learning Classification, Voxel-Based Morphometry (VBM)

Disclosure: Nothing to disclose.

W41. Moderating Effects of the FK506 Binding Protein 5 (FKBP5) Gene on Cortisol Reactivity and Amygdala Volume in Maltreated Children Aged 3-5 Years

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Background: The FK506 binding protein 5 (FKBP5) gene interacts with childhood trauma to predict neurobiological phenotypes and psychiatric disorders in adults. However, the immediate neurobiological impact of maltreatment and its moderation by FKBP5 gene variants in early development is largely unknown.

Methods: 80 children aged 3-5 years with verified maltreatment within 6 moths and 79 age- and sex-matched controls were genotyped for FKBP5 rs1360780. Maltreatment features were coded using the Maltreatment Classification System. Salivary cortisol concentrations were assessed before and after a cognitive challenge. Amygdala volumes were measured in 46 maltreated children who underwent structural magnetic resonance imaging. Mental health status was obtained by parent report using standard instruments.

Results: FKBP5 rs1360780 T allele carriers with maltreatment exposure exhibited increased cortisol reactivity ($B = .01$, $SE = .01$, $p < 0.01$). Within the sample of maltreated children, T allele carriers exhibited increasing amygdala volume ($B = 14.79$, $SE = 5.18$, $p < 0.01$) as a function of maltreatment severity. Increased amygdala volume predicted symptoms of depression and anxiety.

Conclusions: Maltreatment has profound impact on neurobiological and clinical status in children as young as 3-5 years of age and this impact is moderated by variation in genes relevant for stress regulation. FKBP5 allele status may serve as an early indicator of risk for psychopathology in children exposed to maltreatment and might represent a target for novel intervention strategies.

This work was funded by BMBF 01K13101-A (to CH) and 01K13101-B (to EB)

Keywords: Early Life Stress, Brain Development, HPA Axis, Gene Environment Interaction

Disclosure: Nothing to disclose.

W42. Bidirectional Effect of Early Adversity on Epigenetic Aging in Children: Mediation by C - Reactive Protein and Moderation by FKBP5 Gene and Cortisol Status

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Background: The "epigenetic clock" is a biological age estimate based on DNA methylation patterns that vary with chronological age. Epigenetic age acceleration relative to chronological age may reflect disease risk. Early adversity has been shown to accelerate epigenetic aging in children. We examined the relationship between early adversity and epigenetic aging in children with verified maltreatment exposure and modelled the impact of inflammation, cortisol status, and gene variants relevant for stress regulation, i.e. FKBP5, on epigenetic aging.

Methods: We recruited 118 children aged 3 to 5 years with ($n = 61$) and without ($n = 57$) maltreatment exposure. Saliva was collected, and DNA was extracted. Epigenetic age was estimated using a modified version of Horvath's measure and acceleration/deceleration was computed with regression against chronological age. Children were then classified into groups with age acceleration, age deceleration or age congruency. DNA was further genotyped for the FKBP5 rs1360780 polymorphism. C-reactive protein (CRP) as an indicator of inflammation and cortisol concentrations were measured in saliva. We computed a weighted adversity score based on clinical interviews integrating exposure to various characteristics of maltreatment as well as socioeconomic status.

Results: Children whose epigenetic age deviated from their chronological age (acceleration and deceleration) exhibited higher adversity scores relative to age congruent children ($F = 4.940$; $p = .028$). Notably, both acceleration and deceleration groups reported higher adversity, although the effect was more pronounced for the acceleration group. Statistical modeling yielded a significant conditional indirect effect of adversity on epigenetic aging mediated by CRP, predicting either acceleration or deceleration of epigenetic aging, depending on FKBP5 genotype and cortisol status (total model: $R^2 = .145$; $p = .009$).

Conclusions: Our results provide novel insights into a bidirectional effect of adversity on epigenetic aging and a potential mechanism contributing to this effect. Our results may facilitate early identification of children at differential risk for aging-related disease enabling targeted interventions.

Funded by BMBF 01KR1301A to CH and EBB.

Keywords: Childhood Maltreatment, Epigenetics, FKBP5, Inflammation

Disclosure: Nothing to disclose.

W43. Oxytocin Dependent Reopening of a Social Reward Learning Critical Period

Abstract not included.

W44. Psychiatric Associations With Problematic Internet Use in Children and Adolescents

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Background: Problematic internet use (PIU) among children and adolescents is a growing concern as the negative impact on social, educational and familial function are increasingly appreciated. Long driven by excessive web surfing, online gambling and pornography, the recent boom of social media use has fueled concerns about increases in internet use. Estimated prevalence rates to date vary, typically 1-5%, though some estimates in Asia have exceeded 25% (Christakis, 2009). Not surprisingly, associations with psychopathology are consistently emerging (Lee, 2018; Wu, 2016; Younes, 2016), though studies are commonly limited by factors such as focus on a single disorder, small sample sizes, or a focus on a single reporter (i.e., self, parent). Additionally, the relationship between PIU and substance abuse is largely contended with some research indicating that PIU plays a substitutive role (Fisoun, 2012; Laconi, 2017). Here, we leverage the ongoing, large-scale CMI Healthy Brain Network to examine the associations between PIU, psychopathology and substance use. We further evaluate these associations by informant in order to test the influence of perception of both internet use and psychopathology by parent informants and youth.

Methods: Data were collected from clinically referred youth ($n = 1131$; ages 5-21) participating in the CMI Healthy Brain Network research initiative. Parent and self-report versions of the Internet Addiction Test were used to assess PIU (threshold score = 40 based on prior work by Kim, 2016). DSM-V diagnoses were based on a computerized version of the Kiddie Schedule for Affective Disorders and Schizophrenia. For each diagnosis, multiple regressions were used to identify relationships between diagnosis and problematic internet use including sex, age and collection site as covariates. Dimensional measures of psychopathology that mirrored the DSM-V diagnoses included in this study were also investigated for relationships with PIU using multiple regressions. A prevalence odds ratio was calculated for each diagnosis to facilitate comparison of diagnoses. The Fagerstrom Test for Nicotine Dependence, Fagerstrom Tolerance Questionnaire - Adolescent, Alcohol Use Disorders Identification Test, European School Survey Project on Alcohol and Other Drugs, and the Yale Food Addiction Scale were used to assess self-reported measures of nicotine, alcohol, cannabis and food addiction, respectively.

Results: PIU exhibited significant associations with Depressive Disorders (self-report: $p < 0.005$; parent-report: $p < 0.002$) and ADHD-Combined (ADHD-C) (self: $p < 0.026$; parent: $p < 0.001$) per parent- and self-report. Associations with Learning Disorder (LD) were limited to self-report ($p < 0.018$), while associations with Autism Spectrum Disorders (ASD) ($p < 0.029$) and ADHD-Inattentive (ADHD-I) ($p < 0.001$) were limited to parent-report. Independent of diagnosis, parent-report indicated that males had an increased likelihood of falling in the PIU range ($p < 0.001$). Older age predicted increased PIU for both self- ($p < 0.001$) and parent-report ($p < 0.001$). No significant associations were found between collection site and PIU (self: $p < 0.579$; parent: $p < 0.250$). Prevalence odds ratios were highest among individuals diagnosed with Depressive Disorders (self: 2.28 [1.42-3.66]; parent: 4.12 [2.65-6.41]) and those with ASD (self: 1.60 [1.02-2.50]; parent: 1.48 [1.04-2.12]). Prevalence odds ratios for self-reported PIU ($n = 729$, 171 problematic) were highest among those diagnosed with ADHD-C (1.49 [1.01-2.20]), while the prevalence odds ratios for parent-reported PIU ($n = 1086$, 260 PIU) were highest among those diagnosed with anxiety (1.54 [1.13-2.09]) and ADHD-I (2.07 [1.51-2.83]). Of note, when separated by collection site (Staten Island: $n = 744$), Manhattan: $n = 327$), for parent-reported PIU, only findings for Depressive Disorders (Staten Island: 3.58 [1.99-6.45]; Manhattan: 5.08 [2.49-10.35]) and ADHD-I (Staten Island: 2.08 [1.41-3.06]; Manhattan: 2.16 [1.25-3.73]) were individually identifiable at each of the sites. For self-reported PIU, findings for Depressive Disorders in the Staten Island collection site were significant ($n = 48$ with depression, 2.46 [1.32-4.58]), and trended towards significance ($n = 34$ with depression, 1.93 [0.89-4.21]) for the Manhattan collection site. Finally, there were no significant correlations between PIU and other measures of substance abuse (nicotine (self: $p < 0.899$; parent: $p < 0.682$), alcohol (self: $p < 0.110$; parent: $p < 0.457$), and cannabis (self: $p < 0.310$; parent: $p < 0.295$); there was a significant positive correlation between PIU and self-reported food addiction ($p < 0.001$).

Conclusions: The present work confirmed the presence of associations between depression and PIU, regardless of informant or data collection site. Future work will address thresholds between problematic and non-problematic internet use, and potential mechanisms for the associations with different forms of psychopathology. Perceptual differences will also be examined to enhance our understanding of self- and parent-recognition of PIU. Finally, implications for studies that address the developmental influences and course of PIU will be described.

Keywords: Internet, Addiction, Depression, Children

Disclosure: Nothing to disclose.

W45. Intranasal Ketamine Use in Autism Spectrum Disorder: A Placebo-Controlled Crossover Pilot Study

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Background: To address the need to develop effective treatments targeting core impairments of Autism Spectrum Disorder (ASD),

we are completing a double-blind, placebo-controlled crossover pilot study of intranasal (IN) ketamine in 24 individuals with ASD ages 12-30 years. We will present initial study findings including review of study methodology, initial pharmacokinetic (PK) results, initial analysis of primary outcome measures, and review of adverse effects.

Methods: In this cross-over study, participants receive 2 doses of IN ketamine in ascending doses of 30 mg and 50 mg and 2 doses of IN placebo (saline). Participants are monitored for adverse effects (AE) for a minimum of 3 h post-dose. The Clinician Administered Dissociative Status Scale and the Repeatable Battery for Assessment of Neurological Status are completed post-dose to assess for psycho-mimetic and cognitive impact of drug. Study primary outcomes are the Social Withdraw subscale of the Aberrant Behavior Checklist (ABC-SW) and the Clinical Global Impressions Improvement scale completed post-dose and at study conclusion. Three plasma PK samples are drawn post-dose.

Results: Independent sample t tests will be applied for analysis of continuous variables including the Primary ABC-SW measure. For dichotomous outcomes we will use the Fisher's Exact version of the Mainland-Gart test for binary outcomes in a 2X2 crossover. The placebo change from baseline will be compared at each of the active dose levels using a paired analysis. Fisher's Exact Test will be used to analyze AE occurrence in the two groups. Ketamine and norketamine PK concentrations will be determined via low volume, validated liquid chromatography tandem mass spectrometry assay. Concentration data will be analyzed by compartmental and noncompartmental pharmacokinetic analysis with WinNonlin using a weighed least-squares algorithm. Population PK analysis will be conducted using NONMEM version 7.2.0. Parameter estimates generated will include Cmax, total body clearance, distribution and elimination half-lives, volume of distribution and area under the curve.

Conclusions: This innovative approach to investigation of IN ketamine in ASD will provide valuable safety, PK, and outcome data. Results of this study will influence future large-scale study of IN ketamine in ASD.

Keywords: Autism Spectrum Disorders, Ketamine, Intranasal Ketamine

Disclosure: Nothing to disclose.

W46. Psychometric Properties of the Patient Health Questionnaire-9 Modified for Major Depressive Disorder in Adolescents

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Background: The Patient Health Questionnaire-9 Modified (PHQ-9M) is a self-report tool to assess the presence and severity of depressive symptoms. Despite widespread use in primary care clinics and psychiatric settings, the PHQ-9M has not been validated and its psychometric properties are inadequately understood in adolescent populations. This project sought to examine the psychometrics of the PHQ-9M in treatment-seeking, depressed adolescents presenting to a psychopharmacology clinic who were concurrently assessed with the Children's Depression Rating Scale Revised (CDRS-R) and Quick Inventory of Depressive Symptomatology Adolescent Self-Report (QIDS-A17-SR).

Methods: Adolescents (N = 160) aged 13-18 years with a diagnosis of major depressive disorder (MDD) based on a clinical interview and semi-structured interview with the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-PL) were assessed for depressive symptoms severity with the PHQ-9M, CDRS-R (adolescent interview only) and QIDS-A17-SR assessments at baseline, 4 weeks, and 8 weeks. Classical Test Theory analysis was used to evaluate the internal consistency and dimensionality of the PHQ-9M. Convergent validity was evaluated via intraclass correlations of the PHQ-9M with the CDRS-R and QIDS-A17-SR. Sensitivity to treatment response was also evaluated.

Results: The internal consistency (Cronbach's coefficient alpha) at baseline, week 4, and week 8 was 0.879, 0.859, and 0.827 for PHQ-9M; 0.739, 0.835 and 0.867 for CDRS-R; and 0.712, 0.777 and 0.804 for QIDS-A17-SR, respectively. The PHQ-9M had moderate convergent validity with the CDRS-R, but good convergent validity with the QIDS-A17-SR. The PHQ-9M was less sensitive to changes in symptom severity compared to both the CDRS-R and QIDS-A17-SR.

Conclusions: The PHQ-9M appears to be a valid and reliable assessment tool of depressive symptom severity in a psychiatric clinic setting. However, its utility as a treatment outcome measure may be limited when compared to other available rating scales.

Keywords: Adolescent, Adolescent Depression, Clinical Trial Rating Methods, Rating Scales

Disclosure: AssureRX Health, Grant, Self, NeuroStar Advanced Therapy, Grant, Self, NeuroSync, Grant, Self

W47. Do Isomers Matter in ADHD? Reverse Microdialysis Studies of d-, l-, & d,l-Amphetamine-Evoked Dopamine and Norepinephrine Release in the Rat Nucleus Accumbens and Prefrontal Cortex

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Background: There are only a few research studies and case reports showing differences in efficacy and side effects of dextroamphetamine and racemic amphetamine products in children and adults with ADHD. Mixed amphetamine salts (Adderall®), which contains 25% l-amphetamine, has been used since the early 1990s and more recently 50/50 d,l-amphetamine (Evekeo) has FDA approval for ADHD. There is not yet a good understanding of how l-amphetamine works differentially from d-amphetamine. Our hypothesis is that l-amphetamine and d-amphetamine will demonstrate difference on evoked dopamine (DA) and norepinephrine (NE) release in critical brain regions implicated in ADHD.

Methods: Reverse microdialysis was performed in the nucleus accumbens and prefrontal cortex of 30 anesthetized male Fischer 344 rats (3-6 months old to measure amphetamine-evoked release of DA and NE. After perfusing the brain with aCSF for 60 mins, clinically relevant doses (1 μM) of 100% d-amphetamine, 50/50 d,l-amphetamine and 100% l-amphetamine was applied to perfusing brain areas at 0.75ul/min for 120 minutes, followed by aCSF for 60 mins. Samples were analyzed using HPLC with electrochemical detection. Blinding was used to minimize bias. Data were analyzed by analysis of variance (ANOVA) statistics with Sidak's and Tukey's corrections for multiple comparisons.

Results: DA overflow in the prefrontal cortex shows a significant increase for DA between l and dl isomers 140 minutes after introduction of amphetamine ($p = 0.0308$). There was no significant difference between l, dl and d amphetamine isomers, at any time points for NE overflow in prefrontal cortex. NE and DA overflow in the Nucleus Accumbens shows significant increases

for DA over NE for each isomer. DA overflow, using combined area under the curves (AUC (0-inf)) measures, is significantly greater for the d (100) vs. l (100) isomers and d (100) vs. dl (50/50) in NAc ($p < 0.0001$, $p = 0.0031$ respectively. N-5; One-way ANOVA, Tukey's posthoc).

Conclusions: These data support the hypothesis that straight d-, straight l-, and d,l-amphetamine produce differential DA and NE release in critical areas of the rat brain implicated in ADHD. The potential implications of different isomers for ADHD patients as well as side effect profiles of these neurobiological differences will be discussed.

Keywords: ADHD, Amphetamine, Microdialysis

Disclosure: Arbor Pharmaceuticals, Grant

W48. Clinical and Genetic Rett Syndrome Variants are Defined by Stable Electrophysiological Profiles

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Background: Rett Syndrome (RTT) is a rare and complex neurodevelopmental disorder associated with genetic abnormalities in synaptic regulation and is frequently associated with epilepsy. Despite increasing recognition of the clinical heterogeneity of the condition and its variants, namely Hanefeld and Zapella/Preserved Speech Variant, the link between causative mutations and the observed clinic phenotype remains unclear. Electrophysiological parameters measured with quantitative analysis of electroencephalogram (EEG) recordings may act as endophenotypes between the underlying genetic abnormalities and clinical presentation of RTT variants.

Methods: Using a large cohort ($n = 42$) of Rett Syndrome patients between 3-15 years old, we analysed the electrophysiological profiles of RTT variants considering clinical presentations such as epilepsy, and treatment-resistant epilepsy. The distribution of spectral power and inter-electrode coherence measures were derived from continuous resting-state EEG recordings.

Results: We demonstrate the potential role for neural network architecture as an intermediate phenotype in RTT and its variants. MeCP2 and CDKL5 genetic variants of RTT are characterised by discrete patterns of inter-electrode coherence and features of these patterns are associated with specific clinical phenotypes. The quantitative analysis of these electrophysiological features reveals a role of occipito-temporal networks in RTT variants, further elucidating the underlying disease mechanisms. Evaluation of the features associated with comorbid epilepsy reveal patterns of abnormal hemispheric power distribution and network dysfunction associated with epilepsy status and treatment responsiveness.

We further demonstrate that the network abnormalities are significantly associated to RTT variants and are stable over time, suggesting a potential role for electrophysiological features as useful biomarkers in RTT.

Conclusions: Functional network architecture appears to be a stable intermediary between genetic abnormalities of synaptic function and the resulting clinical phenotype. Electrophysiological analysis of network-level features therefore represents a potentially valuable method for the further investigation of RTT and related disorders and offers a non-invasive method for the objective assessment and classification of RTT for determination of diagnosis and prognosis in a clinical setting.

Keywords: Rett Syndrome, MeCP2, EEG

Disclosure: Nothing to disclose.

W49. Protective Role of Maternal Choline on Prenatal Marijuana's Adverse Effects on the Fetus

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Background: Marijuana use is increasingly common in pregnancy. It is promoted by the marijuana community to alleviate morning sickness. Maternal use adversely affects fetal brain development and subsequent childhood behavior including adolescent marijuana use. This study assessed whether higher maternal levels of choline, an essential nutrient for fetal brain development, mitigate early adverse effects of marijuana.

Methods: Observational study with prenatal assessments of maternal marijuana use and choline levels and postnatal assessments of infant neurophysiology and behavior in a public hospital obstetrics and midwifery service at Denver Health Medical Center. Of 316 mothers approached, 201 consented, and 162 brought their newborns for neurophysiological recording at 1 month. At one year, 136 reported their child's behavior. Maternal self-report of marijuana use at various stages of gestation, along with urine toxicology, were used to assess use. The planned outcomes were fetal development of cerebral inhibition, measured by newborn P50 auditory evoked potential inhibition, and subsequent childhood attention and related behavior at 1 year, measured by the Regulation Index of the Infant Behavior Questionnaire.

Results: Forty percent of mothers used marijuana during early gestation. Women who stopped marijuana at 4 weeks or sooner in gestation had children who were similar physiologically and behaviorally to children of women who had never used marijuana. Use at 10 weeks gestation and later by 15% of mothers adversely affected fetal development of central nervous system inhibition. The effect was ameliorated in children of women who had higher levels of choline. At one year of age, the children who had gestational exposure to marijuana, but whose mothers also had higher levels of choline (> 7 microM), had better self-regulation than children exposed to marijuana whose mothers had lower choline levels ($d' = 1.07$). Higher choline levels improved children's duration of attention, satisfaction with quiet play with toys, and cuddling and responsiveness to parents.

Conclusions: Marijuana use during pregnancy, especially after 4 weeks gestation, is likely to adversely affect fetal brain development, with poor self-regulation manifest later in childhood. This effect can be prevented by stopping marijuana use. However, adverse effects may also be mitigated by higher maternal choline levels in the early second trimester.

Keywords: Prenatal Exposure, Marijuana, Cholinergic System

Disclosure: Nothing to disclose.

W50. Prefrontal Parvalbumin Interneurons Require Juvenile Social Experience to Establish Adult Social Behavior

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Background: Social isolation during developmental critical windows could be highly detrimental to proper functioning of mature prefrontal cortex (PFC) and establishment of appropriate adult behaviors. However, the specific circuits that undergo social

experience-dependent maturation to regulate social behavior development are poorly understood. Social processing is a domain that is commonly dysregulated in psychiatric disorders and is poorly treated by available psychiatric medications. In humans and rodents, portions of the evolutionarily conserved medial prefrontal cortex (mPFC) are part of a network that regulates social behavior. Many disorders with shared social processing deficits show impairments in inhibitory neurotransmission within the brain, particularly in the mPFC, suggesting a role for PFC inhibitory action in regulating social behavior. Parvalbumin expressing interneurons (PVIs) are one of the major subclasses of inhibitory neurons, implicated in psychiatric disorders. Here we aim to examine a contribution of PVIs in mPFC for social behavior development in mice.

Methods: We use juvenile social isolation (jSI) during a 2-week sensitive window immediately following weaning and test social behavior in adult male mice ($n = 9$-12 mice) using the 3-chamber test and reciprocal interaction test. To investigate the causal contribution of mPFC-PVIs in social behavior of adult mice, we leveraged chemogenetic technologies. We selectively expressed hM4Di, an inhibitory DREADD (Designer Receptor Exclusively Activated by Designer Drugs), or hM3Dq an excitatory DREADD in the adult mPFC-PVIs and manipulated mPFC-PVI activity acutely using the selective DREADD agonist, Clozapine-N-oxide (CNO). To test the activity of mPFC-PVIs in response to social experience we used in vivo imaging of calcium transients by fiber photometry.

Results: Electrophysiological recordings from adult mPFC-PVIs revealed that juvenile social isolation leads to reduced intrinsic excitability ($p < 0.05$) and input drives ($p < 0.001$), suggesting juvenile social experience is required for proper activation of mPFC-PVIs in adulthood. Real time in vivo imaging of mPFC-PVI activity by fiber photometry demonstrated that adult mPFC-PVIs increase their activity prior to active social bouts in group housed ($p < 0.05$), but not in jSI mice whose active social bouts are significantly reduced compared to group housed controls. Acute chemogenetic suppression of mPFC-PVI activity revealed that normal social behavior ($p = 0.01$) but not anxiety related behavior requires physiological mPFC-PVI activity. Conversely, chemogenetic restoration of mPFC-PVIs activity in the adult animal selectively rescued juvenile isolation-induced social deficits ($p = 0.02$).

Conclusions: These results demonstrate that PVI development in the juvenile mPFC is critically linked to long-term impacts on social behavior. Our study implicates mPFC PVIs as promising cellular targets for future therapeutic development on social impairments in neurodevelopmental and psychiatric disorders.

Keywords: Social Behavior, Medial Prefrontal Cortex, Adolescence, Parvalbumin Neurons

Disclosure: Nothing to disclose.

W51. Single and Multiple Dose Safety, Tolerability and Pharmacokinetics of the Selective M1 Receptor Partial Agonist HTL0018318 in Healthy Volunteers

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Background: The cholinergic neurons of the basal forebrain and medial septum provide the major source of cholinergic innervation to the neocortex and hippocampus and play a critical role modulating cognitive processes such as attention, learning and memory, in part through activation of post-synaptic M1 receptors. It is widely accepted that Alzheimer's disease (AD) is associated with significant early and progressive loss of cholinergic neurons. Cholinesterase inhibitors including donepezil have modest efficacy, potentially because they target degenerating pre-synaptic cholinergic neurons. An alternative and potentially more effective strategy is to target post-synaptic M1 receptors which are relatively preserved in AD. Muscarinic receptor agonists including the M1/M4 agonist xanomeline and the M1 orthosteric agonist GSK1034702 have shown promising early clinical effects but were not further developed due to gastrointestinal and cardiovascular adverse events (AEs).

HTL0018318 is a selective M1 agonist currently under development for the symptomatic treatment of cognitive impairment in dementias including AD and Lewy Body Dementia (LBD). The objective of this study was to examine the single and multiple dose safety, tolerability, pharmacokinetics of HTL0018318 in healthy younger adult and elderly subjects. Pharmacodynamic biomarkers were also assessed but are not presented here.

Methods: The single ascending dose (SAD) study was a single centre, randomized, double-blind, placebo-controlled, sequential, single ascending oral (solution) dose study. HTL0018318 was administered in 5 cohorts of 8 healthy younger adult subjects in ascending dose levels of 1 mg, 3 mg, 9 mg, 20 mg and 35 mg and elderly subjects in ascending dose levels of 9 mg, 15 mg, 23 mg, 30 mg and 35 mg. Effect of food and CSF pharmacokinetics were examined following the 20 mg dose. The multiple ascending dose (MAD) study was a single centre, randomised, double-blind, placebo-controlled, sequential, multiple ascending oral (solution) dose study. HTL0018318 was administered in 3 cohorts of 12 healthy younger adult subjects dosed at 15 mg/day, 20 mg/day and 25 mg/day once daily for 10 days, and 3 cohorts of 12 healthy elderly subjects dosed at 15 mg/day, 20 mg/day and 25 mg/day once daily for 10 days. One elderly cohort was dosed at 35 mg using a titration regimen (5 days on 20 mg/day and 10 days on 35 mg/day).

Results: Pharmacokinetics of HTL0018318 were well-characterized in all subjects at all single doses. Exposure in terms of Cmax and AUC was dose-proportional. Absorption was rapid with a typical Tmax of 1.0-1.5 h post-dose and an apparent mean half-life of 12-16 h. HTL0018318 was found to distribute into CSF (CSF:plasma ratio≈30%). There was no food effect on AUC or half-life of HTL0018318. Single doses of HTL0018318 were associated with mild dose-related AEs (with low incidence) in both younger and elderly subjects. The most frequently reported cholinergic AEs included hypersalivation, hyperhidrosis and increases in blood pressure, particularly following the 35 mg dose (younger adult) and 23 mg and 35 mg doses (elderly). In younger adult subjects, doses up to 20 mg were not associated with changes in systolic and diastolic blood pressure and heart rate. However, the 35 mg dose was associated with an increase in mean systolic and diastolic blood pressure (up to 10 mmHg) and mean heart rate (up to 9.8bpm). In elderly subjects, significant increases in mean systolic and diastolic blood pressure (up to 11.9 mmHg) and mean heart rate (up to 6.3bpm) were observed in the 15-35 mg dose range, with no clear evidence of dose-dependency.

Pharmacokinetics of HTL0018318 were well-characterized in all subjects after multiple doses (Figure 1). The Inter-individual variability in exposure was moderate (6-46 %CV covering Cmax and AUC0-24h). HTL0018318 in repeated administration up to 35 mg/day for 10 days was generally well-tolerated, with mild AEs (with low incidence) and some evidence for dose-dependency. The most frequently reported cholinergic AEs included hyperhidrosis, chills, cold sweat, headache, somnolence and nausea, particularly following the 25 mg dose (young adult) and 25 and 35 mg doses (elderly). Repeated administration HTL0018318 over 10 days was associated with some small statistically significant increases in blood pressure on day 1 (up to 8.7 mmHg) compared to placebo with a decline in this difference with continued dosing.

There were no consistent or clear dose-response relationships. HTL0018318 caused small increases in mean heart rate (up to 10bpm), although these increases were in the context of overall decreases in mean heart rate (i.e. smaller decreases with HTL0018318 relative to the placebo decrease).

There were no clinically significant observations or changes in blood and urine laboratory values or abnormalities in the ECGs and Holter assessments following both single and multiple ascending doses up to 35 mg.

Conclusions: HTL0018318 showed well characterised pharmacokinetics and following single and multiple doses over 10 days were generally well tolerated in the dose range studied. The initial increase in blood pressure following single doses tended to decline with repeated dosing while increases in heart rate were small relative to baseline. These findings provide encouraging safety and pharmacokinetic data in support of the development of HTL0018318 as a symptomatic treatment for cognitive impairment in Dementia.

Keywords: M1 and M4 Muscarinic Receptors, Phase 1, Safety, Pharmacokinetics, Dementia

Disclosure: Sosei Heptares, Employee

W52. Blood Biomarkers for Possible Early Detection of Risk for Alzheimer Disease (AD)

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Background: AD is a clear and present danger to older adults and has a profound socio-economic impact. Early identification of individuals at risk may open the door to preventive approaches. Memory dysfunction is a key feature of AD. We propose to identify blood biomarkers that track a relevant related quantitative phenotype, the retention measure in Hopkins Verbal Learning Task (HVLT).

Methods: Previous work by our group has identified blood gene expression biomarkers that track suicidal ideation using longitudinal within-subject designs, validated them in suicide completers, and tested them in independent cohorts for ability to assess state (suicidal ideation), and ability to predict trait (future hospitalizations for suicidality) (Le-Niculescu et al. Mol. Psychiatry 2013, Niculescu et al. Mol. Psychiatry 2015) (Levey et al. Mol. Psychiatry 2016) (Niculescu et al. Mol. Psychiatry 2017). Those biomarkers were also useful in pharmacogenomic and drug repurposing analyses. We endeavored to use a similar approach to identify biomarkers for the memory measure of retention, and study how predictive they are of future conversion to dementia, particularly mild cognitive impairment (MCI) and AD. We conducted our studies in an already collected by us longitudinal cohort of psychiatric patients, a population enriched in memory retention abnormalities. A subgroup of them ($n = 298$) have blood gene expression data at multiple testing visits, and are deeply phenotyped at each visit, including with HVLT.

Results: First, we investigated whether blood gene expression biomarkers can be identified that track memory retention using a powerful within –subject design in a cohort of subjects who display at least a 20% change in the measure between different visits ($n = 129$), normalized (Z-scored) across genders and various psychiatric diagnoses. Second, we used a Convergent Functional Genomics approach to prioritize the candidate biomarkers in the first step, using published literature evidence (genetic, gene expression and proteomic) for involvement in AD. Third, we examined in an independent cohort ($n = 169$) from the one used for discovery whether the biomarkers prioritized in step 2 are: 1. predictive of memory retention measure (state), and 2.predictive of a future clinical diagnosis of dementia (MCI, AD, other) (trait), using electronic medical records follow-up data of our study participants (up to 12 years from initial visit so far).

Conclusions: Pending additional replication larger independent cohorts, this work has identified novel candidate biomarkers that are early predictors of future AD. Such biomarkers may aid with risk stratification, drug repurposing and new medication development.

Keywords: Alzheimer's Disease, Dementia, Biomarkers for Risk Assessment

Disclosure: MindX Sciences, Stock / Equity

W53. The Mitochondrial Permeability Transition Pore (mPTP) as a Clinically Relevant Drug Target for Geriatric Memory Disorders and Dementia

Abstract not included.

W54. Selective 5-HT2A Inverse Agonists May Effectively Treat Psychosis Associated With Neurodegenerative Processes Through Control of Pyramidal Cell Excitability

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Background: Dementia-related psychosis (DRP) remains a condition with high unmet medical need that is associated with higher rates of mortality and morbidity than subjects with dementia who do not have psychosis. Despite pathological differences in different types of dementia, psychotic symptoms experienced by patients with dementia are similar. Pimavanserin, a selective 5-HT2A inverse agonist/antagonist improves hallucinations and delusions in subjects with Parkinson's disease and in subjects with Alzheimer's disease. In these patients there was no worsening of motor function, cognition or off target effects such as orthostatic hypotension which may increase hazards for the elderly with dementia. We investigated the mechanistic basis for the beneficial effects on hallucinations and delusions associated with neurodegenerative illnesses regardless of the underlying pathophysiology of the neurodegenerative process.

Methods: Scientific literature was reviewed to elucidate the mechanistic basis for the emergence of hallucinations and delusions across different types of dementia and the role of 5-HT2A receptors for the treatment of hallucinations and delusions in these same dementias. The mechanism ideally should account for amyloid beta (Aβ), hyper-phosphorylated Tau (Tau-P) and alpha synuclein (α-Syn) protein aggregates, vascular disease, and mixed pathologies. The mechanism also should account for dementias where the expression of 5-HT2A receptors is increased or decreased.

Results: A review of the literature supported pyramidal cell hyperexcitability associated with Aβ and Tau-P pathologies. Loss of inhibitory control by GABAergic interneurons was a contributing factor in increased pyramidal cell excitability, either through direct loss of GABAergic interneurons or reduced synaptic contact of GABAergic interneurons with pyramidal cells.

Reduced levels of acetylcholine, dopamine, serotonin and norepinephrine were common in dementias with Aβ, Tau-P, and α-Syn aggregates, likely as a consequence of reduced production from the respective cell bodies of the basal forebrain and brain stem supplying these neurotransmitters. These changes might also contribute to disrupted excitatory/inhibitory balance in cortical pyramidal cell activity and thereby lead to psychotic symptoms.

It has been established that 5-HT2A receptors are most highly expressed in cortical regions used for executive function and processing sensory information, with the highest expression found in cortical pyramidal cells, and lower amounts in GABAergic interneurons. In addition, changes in 5-HT2A expression in various dementias, with both increases (mainly in dementia associated with Parkinson's disease) and decreases (mainly in Alzheimer's disease) noted. A limitation was that generally only overall expression levels of 5-HT2A receptors were reported, and not expression levels within the remaining cells, expression levels within specific cell types, nor expression levels of other receptors. Thus, it could not be determined if the ratio of 5-HT2A expressed in pyramidal cells to other cell types that modulate excitability (e.g. GABAergic interneurons) had changed or if the ratio of 5-HT2A receptors to other receptors that could influence pyramidal cell activity had changed. However, even with loss of pyramidal cells and reduced overall expression of 5-HT2A receptors, studies showing reduced synaptic contact between GABAergic interneurons and pyramidal cells provide a plausible explanation for how the remaining pyramidal cells become hyper-excitable.

Conclusions: Loss of inhibitory control of pyramidal cell excitability is a common feature of many dementias, caused by the effects of protein aggregates on GABAergic interneuron function and viability, and may occur whether the expression of 5-HT2A is increased or decreased. Reduced cortical innervation by ascending monoaminergic neurons is another likely contributing factor to deregulation of pyramidal cell activity. Even when there is pronounced neurodegeneration, the remaining pyramidal cells may be hyper-excitable and still influenced by the activity of 5-HT2A receptors.

We conclude that administration of a selective 5-HT2A antagonist/inverse agonist may be effective in treating hallucinations and delusions across a wide range of dementias. Our conclusions are based on the concept that although the cascades of protein aggregation, neurodegeneration and denervation vary between different dementias, they converge on a common endpoint of cortical pyramidal cell excitability, which is strongly impacted by 5-HT2A receptor activity.

Keywords: Dementia-Related Psychosis, 5-HT2A Receptor, Pyramidal Neuron

Disclosure: ACADIA Pharmaceuticals Inc., Employee, Stock / Equity

W55. Dual Recombinase Fate Mapping Reveals Extensive Co-Expression of Cholinergic and Glutamatergic Markers and Developmental Phenotype Switching in the Central Nervous System

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Background: Exposure to nicotine in utero is associated with altered cognitive function in humans and in rodents, and increased incidence of sudden infant death syndrome due to potential instability of respiratory circuitry. However, how these outcomes might result from nicotine effects on cholinergic neurotransmission is not well understood. Known cholinergic neurons in the central nervous system include the brainstem motor nuclei and several important neuromodulatory systems. Motor neurons and some other CNS neurons appear to use ACh alone as a fast neurotransmitter, but ACh is also produced in neurons that additionally use glutamate as a transmitter. Neurons of this type are found in the ventral medial habenula, which are predominantly glutamatergic and appear to release ACh only in response to high-frequency stimulation (Ren et al., 2011; Hsu et al., 2013; Frahm et al., 2015). Co-expression of glutamatergic and cholinergic markers has also been identified in the striatum (Gras et al., 2008), where glutamate is transported by Vglut3, and in neurons contributing to the regulation of respiratory rhythms in the medulla (Anderson et al., 2016).

Here we have used cre-recombinase mediated genetic fate mapping to identify all developing and mature CNS neurons that express the biosynthetic enzyme for ACh, choline acetyltransferase (ChAT), and an intersectional genetic approach to show which of these neurons also express the subcortical vesicular glutamate transporter Vglut2. In addition, we have used database information to correlate these results with the expression of the vesicular acetylcholine transporter, VAChT, which is also required for ACh-mediated synaptic transmission. These experiments show that the co-expression and sequential expression of cholinergic and glutamatergic markers are much more extensive than previously supposed.

Methods: Cholinergic neurons were identified genetically by crossing a ChatCre transgenic mouse line (ChatIRESCreΔneo, Jax 031661) with a cre-dependent reporter line, Ai14 (Madisen et al., 2010), encoding tdTomato (tdT), which labels both neuronal cell bodies and axons. To determine the developmental onset of tdT expression we examined ChatCre/Ai14 mice at embryonic day 16.5 (E16.5), E18.5, postnatal day 1 (P1), P4, and P14. Immunostaining was used to verify that the ChatCre/Ai14-labeled neurons expressed ChAT protein either in mature neurons or at specific developmental stages. Neurons with co-expression of ACh and glutamate were identified using a dual Cre-Flp recombination strategy using ChatCre, flp-recombinase expressed from the Slc17a6 locus (Vglut2Flp), and a dual reporter strain Ai65, which requires the excision of two transcriptional stops, one flanked by loxp and one flanked by frt, to activate expression of tdT (Harris et al., 2014; Daigle et al., 2018). Because the tandem stop sequences can be excised in either order, expression of the reporter in Ai65 mice may indicate either sequential or simultaneous expression of ChAT and Vglut2 in a given neuron. Gene expression databases for the mouse brain (http://mouse.brain-map.org/) and developing mouse brain (http://developingmouse.brain-map.org/), and antisera for other neurotransmitter markers were also used to characterize the phenotypes of the identified neurons.

Results: As expected, ChatCre induced tdT expression in known cholinergic populations including striatal and basal forebrain cholinergic neurons, the arcuate nucleus, the medial habenula, the pedunculopontine and laterodorsal tegmental systems, brainstem motor nuclei and selected reticular neurons of the medulla. Unexpectedly, tdT expression was observed in multiple other brain regions, including the subiculum of the hypothalamus, ventral thalamus (VM), rostrolateral hypothalamus, the parabigeminal and lateral parabrachial nuclei, specific subsets of precerebellar neurons in the pons and inferior olive, and the cuneate/gracilis nuclei. Careful examination of ChAT protein and mRNA expression in the adult brain revealed low levels of persisting expression in some of these nuclei, but in most of these areas ChAT expression was detected only in developing neurons. Dual recombinase mapping with ChatCre/Vglut2Flp was then used to show that most or all of these transiently ChAT-expressing neurons ultimately use glutamate as their principal neurotransmitter.

Conclusions: These findings show that the extent of co-transmission using ACh and glutamate, particularly in the developing brain, may be more extensive than previously known, and suggest a wider role for cholinergic signaling in the maturation of excitatory CNS circuits. Both nicotinic and muscarinic receptors are candidates for mediating the developmental effects of acetylcholine in developing excitatory circuits.

However, nicotinic mechanisms may have special significance for understanding brain systems and critical windows of development that are vulnerable to exposure to nicotine in utero. For example, effects on the developing precerebellar and respiratory rhythm generation systems could provide a basis for the known association between maternal smoking during pregnancy and sudden infant death syndrome.

Keywords: Acetylcholine, Nicotine, Glutamate, Neurodevelopment, Neurotransmitter Co-Release

Disclosure: Nothing to disclose.

W56. Maternal Immune Activation During Pregnancy is Associated With Microstructural Tissue Organization of the Brain in Neonates

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Background: Maternal immune activation (MIA) during pregnancy is associated with alterations in offspring brain development in preclinical animal models and risk of developmental psychiatric disorders in large-scale epidemiological studies. Yet, translational human studies of MIA in association with early brain development are sparse and have mainly focused on the developing functional connectome. For example, prenatal maternal interleukin-6 (IL-6), a pro-inflammatory cytokine, has been associated with individual differences in the strength of functional connectivity for the salience (insula and anterior cingulate cortex) network and amygdala connectivity to cortical brain regions in neonates. Only one study thus far has related MIA to tissue organization of the brain, which provides the foundation for developing functional networks. The study found that higher levels of maternal IL-6 were associated with reduced development of a fronto-limbic white matter tract in neonates. Expanding our understanding of MIA's association with early tissue organization is an important next step as the previous animal and human studies point to diffuse brain changes. Furthermore, understanding whether the timing of exposure and additional indices of MIA have differing effects on early brain development could help to identify multiple pathways that lead to psychiatric risk. Here, we test the hypothesis that higher levels of MIA as measured by two indices, maternal IL-6 and C-reactive protein (CRP), an acute phase reactant, during the 2nd and 3rd trimesters, are associated with variation in gray and white matter organizational properties in neonates.

Methods: Forty-nine young pregnant women, aged 14 to 19, were recruited from Columbia University Medical Center. They received routine prenatal care and had no major health problems. At 34-37 weeks of gestation, the women underwent diagnostic evaluations and blood draws. IL-6 and CRP were measured using the enzyme-linked immunosorbent assay. For the neonates, diffusion weighted imaging data were acquired on a GE Signa 3 T scanner to measure the directional diffusion of water indexed by fractional anisotropy (FA). All analyses covaried for sex and postmenstrual age at scan.

Results: Higher levels of maternal IL-6 in the 2nd trimester were associated with increased FA values in subcortical regions of both hemispheres, primarily in gray matter of the basal ganglia and thalamus, and diffusely across gray and white matter of the occipital lobe and right anterior temporal lobe. The findings were similar for the 3rd trimester. Higher levels of CRP in the 2nd trimester was associated with mainly decreased FA values diffuse across differing subregions of the frontal and occipital lobes, as well as the anterior limb of the internal capsules, and increased FA values of the posterior limb of the internal capsules of both hemispheres. In the 3rd trimester, the results for CRP were similar to the results from the 2nd trimester, though with more widespread decreases in FA values primarily in the frontal lobes, and the anterior temporal lobe.

Conclusions: In line with preclinical findings, we show that maternal IL-6 and CRP levels are associated with measures of tissue organization in the neonatal brain. Generally, 2nd and 3rd trimester findings are similar across the two immune markers. However, the immune markers demonstrate shared and distinct associations with regional tissue organization. For example, IL-6 is primarily associated with decreases in subcortical gray matter (basal ganglia and thalamus), whereas CRP is primarily associated with tissue organization in the frontal lobes. Both immune markers share associations across the occipital lobes and the anterior temporal lobe. The findings highlight the importance of considering multiple measures of MIA in this emerging area of research, as different immune-brain pathways may contribute to future psychiatric risk. The effects of MIA on the developing brain appear to occur beyond fronto-limbic circuitry, and thus whole brain analyses may help identify specific regions of the brain that warrant further investigation. This is a logical next step because of the widespread brain changes associated with MIA from animal studies and this current study, and from the diverse cognitive functions and psychiatric symptoms that have been associated with MIA.

Keywords: Immune Biomarkers, Prenatal Exposure, Fractional Anisotropy, Infant

Disclosure: Nothing to disclose.

W57. Prenatal Trauma and Neurodevelopment: A Pilot Study of the Impact of Maternal Childhood Trauma on the Infant Brain

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Background: Trauma in one generation can have persistent behavioral and neuropsychological effects upon the next generation. Mechanisms explaining this intergenerational influence include epigenetic modifications, as well as the effects of trauma on parenting (e.g., trauma within one generation influences parenting behaviors with consequent effects on the next generation.) An additional pathway, termed the fetal origins of disease, suggests that maternal experiences, including trauma, influence the intrauterine environment potentially through endocrine and inflammatory changes. The intrauterine environment provides crucial information to the developing fetus improving the offspring's likelihood of survival, but also potentially conferring detrimentally effects on other aspects of development and health.

Here we examined the influence of maternal childhood trauma on fetal brain development using resting state functional MRI (rsfMRI) in sleeping, non-sedated infants. We hypothesized that relative to infants of mothers without a history of childhood trauma, infants of mothers with a trauma history would show altered functional connectivity within limbic regions including the orbitofrontal cortex.

Methods: This pilot study was conducted at Federal University of São Paulo and approved by the National IRB (CONEP), the UNIFESP University IRB and the NYSPI-Columbia University IRB. Pregnant women (mean age: 24.4, + /- 6.5 SD) were recruited during their third trimester and completed a comprehensive psychiatric assessment including the Childhood Trauma Questionnaire (CTQ). We enrolled 32 pregnant women who

experienced childhood trauma (physical, emotional, or sexual trauma as indexed by the CTQ) as well as 32 healthy controls with no history of childhood trauma, matched by age.

From this sample of 64 pregnant women, we obtained resting fMRI scans in 16 infants with maternal trauma exposure (infants + t) and 15 infants without maternal trauma exposure (infants-t). Infants were ~2 weeks old when scanned and scanning was done with a 3 T Phillips Achieva, 8-channel head coil, and no sedation (during natural sleep). Echoplanar imaging was used with the following parameters: TR = 2.3 ms, TE = 0.03 ms, slice thickness 3 mm, with 34 slices with whole brain coverage. One run of 210 volumes (8 min, 3 seconds) was obtained for each infant.

Image preprocessing was performed with SPM12 and the CONN toolbox. Images were motion-corrected, co-registered with an anatomical scan, normalized to an infant template brain, and smoothed with a Gaussian kernel of 6 mm full width at half maximum. Temporal band-pass filtering (0.008–0.09 Hz) was applied. Nuisance regressors included six head motion parameters, and orthogonal fMRI time series extracted using component-based noise correction within each individual's white matter and cerebrospinal fluid. Volumes with excessive head motion were "scrubbed" following standard imaging procedure; if over 20% of volumes required scrubbing, the run was excluded. Usable rsfMRI data were thus obtained in 20 infants (11 infants + t; 9 infants-t).

The resting fMRI time series were then correlated across 90 regions of interest (ROI) from a published infant atlas, generating a 90x90 ROI correlation matrix for each infant participant. Fisher-z transformation was applied. Group-wise comparisons were conducted on all 90x90 connections uses a factorial model with Group as the single factor with two levels (infants + t and infants-t) and age, sex, and birth weight as covariates. False discovery rate (pfdr < 0.05) was used to correct for multiple comparisons.

Results: Relative to infants-t, infants + t showed decreased connectivity between the left posterior insula and the left inferior, middle, and superior orbitofrontal cortices (OFC) (all tests pfdr < 0.05). Infants + t also showed reduced connectivity between the superior and middle temporal gyri bilaterally and the frontal lobes bilaterally (all tests pfdr < 0.05).

Exploratory analyses indicated that for the infants + t reduced connectivity between the left posterior insula and the left inferior OFC correlated inversely with maternal exposure to childhood physical trauma (r = -0.67, p = 0.02).

Conclusions: This pilot study suggests that among very low-income families, maternal experiences of childhood trauma influence fetal brain development as indicated by reductions in functional connectivity within limbic regions including the OFC and posterior insular cortex. These brain regions have previously been implicated in impulsivity and risky decision making later in life and are consistent with observational studies suggesting an association between prenatal maternal trauma and ADHD and other externalizing behaviors. Subsequent research may examine the significance of these infant MRI findings in light of more recent maternal traumatic experiences and other potentially relevant factors. Also, next steps should include follow up behavioral and clinical assessments as the infant mature and explore potential mediators by which maternal trauma influences fetal neurodevelopment, such as maternal inflammatory markers or stress hormones. Understanding how maternal trauma alters fetal brain development may help identify steps to curtail adverse intergenerational effects of trauma.

Keywords: Childhood Trauma, Infant, Fetal Programming, fMRI Negative Affective Stimuli, Sex Differences, Prenatal Stress-Immune Model, Stress-Immune Dysregulation, Orbitofrontal Cortex, Insula

Disclosure: Nothing to disclose.

W58. The Type of Prenatal Distress Differentially Affects Hippocampal Functional Connectivity in Human Neonates

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Background: Maternal prenatal distress—typically assessed as depression, anxiety, or stress—is a risk factor for children's future psychiatric disorders including autism, ADHD, depression, and substance use. Data suggest that prenatal exposure to maternal distress is associated with altered brain development of children and adolescents. Consistently, the hippocampus has been shown to be vulnerable to high levels of maternal distress across preclinical and human studies. More recently, the effects of prenatal maternal distress on offspring brain development have been highlighted to be identifiable as early as the fetal to infancy periods. These findings have expanded our knowledge of a critical developmental period and of factors contributing to the intergenerational transmission of psychiatric symptoms. Nevertheless, distress is multifaceted. Previous studies typically have relied on a single assessment approach. The goal of the current study is to determine whether various types of maternal prenatal distress affect neonatal functional connectivity in similar or unique ways.

Methods: Forty-five young pregnant women at high risk for life distress, aged 14 to 19, were recruited from Columbia University Medical Center. They received routine prenatal care and had no major health problems. At 34-37 weeks of gestation, the women provided self-report psychological stress assessment including the Perceived Stress Scale (PSS), Reynolds Adolescent Depression Scale (RADS), and Prenatal Distress Questionnaire (PDQ). For the neonates, resting-state functional MRI data were acquired on a GE Signa 3 T scanner. Standard seed connectivity from the right and left hippocampus was performed. Prenatal distress measures were correlated with connectivity while controlling for postmenstrual age (PMA) at scan and sex. All results are at p < 0.05, corrected for multiple comparisons.

Results: All neonates were appropriate for gestational age (birth weight: 3206.9 ± 461.3 g, gestational at birth: 39.3 ± 1.3 weeks) and were scanned at 42.4 ± 1.6 weeks postmenstrual age. The majority of participants were male (68.8%). With higher levels of maternal scores on the PSS, neonates exhibited weaker connectivity between the left hippocampus and dorsal anterior cingulate cortex (dACC), between the right hippocampus and the dACC, and between the right hippocampus and the mid cingulate cortex (MCC), and stronger connectivity between the right hippocampus and left fusiform gyrus. With higher levels of maternal scores on the RADS, neonates exhibited weaker connectivity between the left hippocampus and posterior cingulate cortex (PCC) and between the right hippocampus and precuneus. With higher levels of maternal scores on the PDQ, neonates exhibited stronger connectivity between the left hippocampus and right superior temporal sulcus (STS).

Conclusions: Using multiple measures of prenatal maternal distress, we demonstrate mainly weaker functional connectivity between the hippocampus and several cortical regions in the neonatal brain. We show associations between perceived stress and hippocampal – dACC/MCC connectivity; between depressive symptoms and hippocampal – PCC/precuneus connectivity; and between pregnancy distress and hippocampal – STS connectivity. These connectivity patterns suggest functional differences that are unique to the type of prenatal maternal distress. Perceived stress, an index of life stress in the past month that may be consistent with the RDoC domain of sustained threat, affects connectivity in networks associated with salience detection and emotion regulation. Depressive symptoms, an index of chronic distress and the RDoC domain of

loss affect connectivity in networks involved in internal attention. Pregnancy-related stress, an index of state-specific stress, affects connectivity in brain regions involved in language and memory. The current study highlights the importance of considering multiple facets of distress. Future studies are necessary to examine these hippocampal connectivity patterns to toddler outcomes, as they will establish the corresponding behavioral phenotypes in early life that may contribute to risk for future psychiatric symptoms and an intergenerational transmission of familial pattern of affect dysregulation.

Keywords: Neonatal, Resting State Functional Connectivity, Perinatal Stress

Disclosure: Nothing to disclose.

W59. A Novel Translational Biomarker of Intergenerational Risk for Neurodevelopmental Reprogramming

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Background: Maternal stress experience during pregnancy produces lasting effects on the developing brain, increasing subsequent risk for neurodevelopmental and neuropsychiatric disorders throughout life. As neurodevelopmental disorders are multifactorial and exhibit a high degree of comorbidity, novel discovery-based approaches may facilitate identification of novel mechanisms through which fetal antecedents contribute to brain development and health outcomes later in life. Using our well-established mouse model of early prenatal stress, in which exposed males exhibit lasting reprogramming of hypothalamic circuits controlling neuroendocrine response to stress and metabolism, we previously examined the hypothesis that the maternal vaginal microbiome mediates the effects of prenatal stress. As newborns acquire the initial community of microbiota from the mother during birth, this intergenerational transmission of microbiota is essential for establishing the bidirectional communication between the immune system and the brain. To assess the mechanistic contribution of the stress-altered vaginal microbiome on offspring physiology and behavior, we developed a novel transplantation method in which mouse pups were delivered by cesarean section, thereby preventing natural colonization, and then transplanted with vaginal microbiota via orogastric gavage. Transplantation of vaginal microbiota from stressed dams into naïve pups delivered by cesarean section recapitulated the prenatal stress phenotype. including reduced body weight, increased corticosterone response to acute stressors, and upregulation of immune and inflammatory gene signatures in the paraventricular nucleus of the hypothalamus. However, transplantation of control vaginal microbiota into prenatally stressed pups delivered by cesarean section did not rescue the prenatal-stress phenotype. The inability to rescue the prenatal stress phenotype was dependent on transcriptional reprogramming to pathways involved in the regulation of innate immunity in the fetal gut and brain. Further, these results suggest that the prenatal immune environment have direct effect on neurodevelopmental reprogramming. Thus, we examined the hypothesis that sex-specific neuroimmune development is influenced by stress effects on the maternal gut microbiome.

Methods: We used a combination of genomic, flow cytometric, mass cytometric and pharmacological manipulations to assess the stress-reprogramming of the immune compartment of the fetal brain via the maternal gut microbiome. Reconstitution experiments were used to examine the casual contribution of maternal gut microbiome to rescue aspects of the prenatal stress phenotype in adulthood. To establish translational relevance of our mouse model, pregnant women who had experienced either a low (<2) or high (>2) number of adverse childhood events (ACEs) during the preadolescent window were recruited at 21 to 32 weeks of pregnancy. Gut microbiota composition, pro-inflammatory cytokine profiles, and cortisol levels following acute stress were measured in low and high ACE pregnant women.

Results: Maternal stress exposure increased the detection of inflammation-associated microbiota and disrupted microbiota production of metabolites necessary for brain development. Comparison of metabolites from maternal and fetal tissues demonstrated stress-mediated decreases in key metabolites in maternal cecum and fetal brain. As these metabolites regulate innate immune development, we next determined how altered metabolite availability impacts the fetal brain immune compartment using high dimensional single-cell mapping and multicolor flow cytometry. Analysis revealed sex-specific changes in the frequency and activation patterns of resident and infiltrating immune cells in the fetal brain. Sex-specific modifications to chromatin accessibility and transcriptomes of fetal immune cell populations were also assessed. Similar to our results in our prenatal stress mouse model, the maternal gut microbiome was significantly changed in high ACE women relative to low ACE women during pregnancy. Further, pro-inflammatory cytokines were positively correlated with inflammation-associated microbiota in high ACE women, providing an important link between early life adversity and peripheral inflammation during pregnancy.

Conclusions: Our translational approach demonstrates that the maternal gut microbiome is a putative biomarker of neurodevelopment that may predict disease risk in offspring. The mouse model has identified key mechanistic points whereby changes in inflammation and metabolites produced by the maternal gut microbiota impact fetal brain development and exert lasting outcomes on offspring physiology and behavior and metabolic function. The human studies demonstrate lasting effects of childhood adversity can also promote inflammation and stress responsivity during pregnancy that similarly associated with disruption to the maternal gut microbiota. As the gut microbiome is easily accessibility, further studies will work to pinpoint biomarkers predictive of disrupted metabolite production and inflammation during pregnancy that may be used to develop interventions or therapies beneficial to fetal brain development.

Keywords: Neurodevelopmental Disorders, Sex Differences, Perinatal Stress, Neuroimmunology, Bioinformatics

Disclosure: Nothing to disclose.

W60. Neurobiology of Food Choice Across the Spectrum of Restrictive Eating

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Background: Anorexia nervosa (AN) is a severe disorder with a mortality rate the highest of any psychiatric illness. The disorder is characterized, in part, by persistent dietary restriction leading to starvation. The choice to eat low-calorie, low-fat foods is linked to longer-term outcome and is highly resistant to change. Growing identification of the neural mechanisms of choice among healthy individuals provides an opportunity to improve understanding of the neural underpinnings of this type of maladaptive behavior in AN. In an initial study, we demonstrated that among AN, but not healthy controls (HC), active decision-making around food choice was related to neural activation in the dorsal striatum. We aimed, first, to replicate and extend this finding by examining choice-

related activation changes with treatment, and second, to evaluate eating behavior and neural activation across the spectrum from adaptive to maladaptive. We hypothesized that 1) proportion of high fat choices and neural activation in the dorsal striatum during choice would differ between AN and HC; 2) these measures would begin to normalize with weight restoration; and 3) choice related activation in the dorsal striatum would increase per diagnostic group in proportion to the degree of dietary restriction among AN, subthreshold AN (sAN, defined as clinically significant restrictive intake with BMI ≥ 18.5 kg/m2 for 3 months), dieting HC (HC-D) and HC.

Methods: We administered a computer-based Food Choice Task with functional MRI to women across this spectrum of dietary restriction. Participants first rated 76 food images (high and low-fat items) for Healthiness and Tastiness; an item rated neutral in both blocks was then selected as the Reference item. On each of 76 subsequent trials, participants were asked to choose between the Reference item and an alternate food image. The next day, a laboratory multi-item meal was administered. Food items were weighed before and after and caloric intake was calculated. Proportion of high-fat foods selected in the Choice block of the task was compared before and after treatment using repeated measures ANOVA and between groups using one-way ANOVA. Parametric analyses were used to measure neural activation associated with choice. To replicate assessment of task validity, the association between task choices and caloric intake was tested with Pearson's correlation. Study enrollment will be completed in Fall, 2018.

Results: Participants, to date, include individuals with AN ($n = 33$), sAN ($n = 17$), HC-D ($n = 21$) and HC ($n = 36$). Across AN versus HC, there was persistent disturbance and no significant change with weight restoration in task-based food choices (Group: $F1,40 = 7.6$, $p = 0.009$; Time: $F1,40 = 2.9$, $p = 0.096$) or in the laboratory meal (Group: $F1,44 = 6.6$, $p = 0.01$; Time: $F1,44 = 0.2$, $p = 0.67$). Preliminary fMRI analyses indicated that AN engage dorsal striatum during food choice, while HC did not, and this pattern persisted after weight restoration. Across the 4 diagnostic groups, there was a significant difference in proportion of high-fat choices ($F3,145 = 11.2$, $p < 0.001$): patient groups (AN and subthreshold AN) differed significantly from the healthy individuals (HC and HC-D) but not from each other in high-fat food choices. There were significant group differences in caloric intake at the lunch meal ($F3,138 = 7.5$, $p < 0.001$): HC did not differ from HC-D, but did differ from sAN and AN; AN did not differ from sAN or HC-D.

Conclusions: These preliminary analyses replicate the finding that individuals with AN engage different neural systems than HC when making decisions about food and indicate that these behavioral and neural patterns are remarkably persistent. Furthermore, the patterns of restrictive choices across the spectrum indicate a clinically meaningful distinction between dieting and pathological dietary restriction. The absence of meaningful change with weight restoration highlights the need for new mechanism-based treatment interventions.

Keywords: Anorexia Nervosa, Eating Disorders, Cognitive Neuroscience, Habits

Disclosure: UpToDate, Royalties

W61. Novel Behavioural and Neural Evidence for Reduced Satiation and Enhanced Reward Responses to Food Stimuli in Individuals With High Attention Deficit Hyperactivity Disorder (ADHD) Symptoms

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Background: Individuals with Attention Deficit Hyperactivity Disorder (ADHD) may be at risk of developing disordered eating, particularly overeating and binge-like eating. However, little is known about the mechanisms that underlie disordered eating in ADHD. The aim of the present study was to assess under laboratory conditions whether eating in the absence of hunger is associated with ADHD symptoms and whether participants scoring highly on a standard ADHD symptom rating scale differ from low scoring participants in their neural responses to food pictures assessed using functional Magnetic Resonance Imaging (fMRI).

Methods: We assessed eating behaviour in young adults with high ADHD symptoms (31 ADHD+; 15 males, 16 females) compared to matched control participants with low ADHD symptoms (27 Controls; 13 males, 14 females). Symptoms of ADHD were assessed using the Conner's Adult ADHD Rating Scale Self Report-Screening Version. Eating behaviour was investigated using laboratory measures of food intake in conjunction with questionnaire measures, including The Binge Eating Scale (BES), the Bulimic Investigatory Test, Edinburgh (BITE) and the Loss of Control over Eating Scale (Brief version). Food intake and meal microstructure were recorded using a Universal Eating Monitor (UEM). The UEM comprises a weighing system and computer software to enable detailed collection and analysis of human eating behaviour that continuously monitors food intake in parallel with measures of appetite and satiety. Participants were offered a pasta meal to eat until satiety. To assess eating in the absence of hunger, twenty minutes later they were offered a snack of palatable cookies and told they could eat as much as they wished. Neural correlates of responses to food pictures were investigated using Blood-Oxygen-Level-Dependent (BOLD) fMRI. Participants viewed images of high and low-calorie foods and control (non-food) items. Images were displayed for 2500 ms and participants were asked to rate the appeal of each image.

Results: The ADHD+ and control groups did not differ in age or BMI, mean BMI was 23.4 (SEM = 0.59) for the ADHD+ group and 22.9 (SEM = 0.64) for the control group but the ADHD+ participants scored significantly higher on questionnaire measures of binge-like eating than the control participants ($t(51) = 3.51$, $p = 0.01$).

The mean score for binge/disinhibited eating was 17.09 (SEM = 1.81) for the control group and 28.70 (SEM = 2.77) for the ADHD+ group. ANOVA with group and sex as factors and BMI as a covariate revealed a significant main effect of group, $F(1, 53) = 11.69$, $p = 0.01$, $np2 = 0.18$, with ADHD+ participants scoring significantly higher than controls ($t(51) = 3.51$, $p = 0.01$). A significant main effect of gender was also observed, $F(1, 53) = 5.35$, $p = 0.03$, $np2 = 0.09$, with females scoring significantly higher than males ($t(51) = 2.11$, $p = 0.04$), but there was no significant interaction between group and gender, $F(1, 53) = 0.02$, $p = 0.90$, $np2 = 0.00$). Total pasta and cookie intake did not differ between groups but the ADHD+ group scored significantly lower than the control group on the Satiation Quotient a measure of the satiating effect of the cookies. The Satiation Quotient, which provides a measure of the satiating effects of a given amount of calories at various time points after an eating episode, was reduced suggesting that the ADHD+ participants found the cookies less filling even though they ate the same amount of food. ADHD+ participants also showed enhanced BOLD fMRI responses to food versus non-food pictures compared to the control group in reward-related brain areas including the ventral tegmental area, caudate nucleus and ventromedial prefrontal cortex (all $p < 0.05$ FWE corrected).

Conclusions: The present results confirm that ADHD symptoms are associated with binge-like eating and provide the first evidence that ADHD symptoms in young adults are associated with disturbances in eating behaviour assessed under laboratory conditions. Neural activation in key reward-related brain areas in

response to viewing food pictures was enhanced in participants with high scores on an ADHD symptom rating scale compared to control participants. This suggests that enhanced responsiveness to food cues may be a mediating mechanism underlying over eating in ADHD. Further investigation of the role of altered reward processes in ADHD may be helpful in developing novel treatments for both ADHD and Binge Eating Disorder. Lisdexamphetamine (Vyvanse®) is approved by the FDA for the treatment of both ADHD and Binge Eating Disorder. Until now it has been unclear how lisdexamphetamine reduces binge eating but our results suggest that one mechanism worthy of further investigation is the potential effects of the drug on food reward processes.

Keywords: Binge Eating Disorder, Attention Deficit Hyperactivity Disorder, Satiation, Reward, fMRI

Disclosure: P1vital Limited, Board Member, P1vital Limited, Employee, P1vital Products Limited, Board Member

W62. Bariatric Surgery Increases Functional and Structural Connectivity Between Dorsolateral Prefrontal Cortex and Anterior Cingulate Cortex in Obese Patients

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Background: Obese individuals show functional abnormalities in brain circuits implicated in reward, motivation, emotion and inhibitory-control under high-calorie (HiCal) food cue stimulation. Bariatric surgery is the most effective intervention for weight reduction in morbid obesity. Neuroimaging studies have reported alterations in homeostatic/hedonic neurocircuits after bariatric surgery, but its effects on frontal-limbic activation and functional connectivity (FC) remains unclear. Prior studies showed that laparoscopic sleeve gastrectomy (LSG) promoted structural recovery of gray- (GM) and white-matter (WM) density, WM integrity and cortical morphometry particularly in frontal regions. However, whether LSG-induced structural connectivity (SC) and its subsequent contribution to brain activity and FC and behavioral changes has been less studied. Here, we employed fMRI and diffusion tensor imaging (DTI) and used a food-cue reactivity task to localize the frontal-limbic regions involved in food cue processing to use these as seed masks to calculate the SC between these regions and their association with brain activation and behavior.

Methods: Twenty-eight obese patients who underwent LSG (SG) and 22 age and sex matched obese controls (Ctr) underwent 3 T MRI. SG group was tested before and one month after LSG, and the Ctr group was tested twice without surgery at a one-month interval. We first conducted a food cue reactivity task fMRI scan (T2*-weighted gradient echo planar imaging sequence in a 3 T GE MRI scanner, TR/TE = 2000/30 ms, 64 x 64 matrix size, 256 x 256 mm2 FOV, 90-degree flip angle, 4 mm3 isotropic resolution and 32 axial slices) after 12-hour fasting. The stimulation consisted of three HiCal and three low-calorie (LoCal) food cue blocks presented in a pseudorandom order. Then, diffusion-weighted images were acquired (a single-shot spin-echo echo-planar-imaging sequence, TR/TE = 9400/84 ms, 128 x 128 matrix size, 256 x 256 mm2 FOV, 2 mm3 isotropic voxels, 75 axial slices). The images underwent slice-timing, head movement correction, co-registration, spatial normalization and smoothing. A general linear model including HiCal and LoCal food cue regressors was constructed. Individual images contrasting between HiCal and LoCal cues were computed and submitted to second-level statistical analysis. Two factors (SG, Ctr) repeated (Baseline, 1 Month Later) ANOVA measures were used to assess the main and interactions effects on brain responses to food cue; regions of interest were identified for subsequent Psychophysiological interaction analyses (PPI) to assess alterations in task-related functional connectivity, and to examine the association with weight loss. For DTI fractional anisotropy (FA), mean, axial and radial diffusivity were calculated and fiber tracking analysis between the ROIs defined based on food-cue reactivity activation were performed. Statistical significance was based on family-wise error (FWE) corrections at the cluster level (PFWE < 0.05) using a minimum cluster size of k = 50 and a cluster forming a threshold of P < 0.001. Mediation analysis was used to assess whether the relationship between changes in BMI and changes in FC was mediated by changes in SC.

Results: LSG significantly decreased brain activation in right dorsolateral prefrontal cortex (DLPFC) involved with executive-control in response to HiCal versus LoCal food cue in the SG group. Further, LSG increased FC of the right DLPFC-ventromedial anterior cingulate cortex (vmACC), and SC between the DLPFC and vmACC. Changes in FA and PPI between DLPFC and vmACC showed a negative correlation with changes in body mass index (BMI), and changes in FA (SC) showed a positive correlation with changes in PPI (FC). In addition, the relationship between the reduction in BMI and the increases in FC between right DLPFC and vmACC was mediated by increases in SC between the right DLPFC and vmACC.

Conclusions: These findings suggest that LSG-induced weight-loss may alter functional connectivity between DLPFC and vmACC by influencing its SC. These changes reflect a strengthening of top-down control after LSG.

Keywords: Obesity, Bariatric Surgery, Dorsolateral Prefrontal Cortex, Anterior Cingulate Cortex, fMRI/Diffusion Tensor Imaging

Disclosure: Nothing to disclose.

W63. Brain Reward Response and Taste Perception Independently Predict Long Term Weight in Anorexia Nervosa

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Background: The eating anorexia nervosa (AN) is a severe psychiatric illness with a high mortality rate. Recent functional magnetic resonance brain imaging studies from our lab have repeatedly shown that the brain reward system is altered in AN. Specifically, during unexpected receipt or omission of rewarding or salient stimuli individuals with AN showed higher brain response compared to controls in striatum and insula. This so-called prediction error (PE) response has been associated with brain dopamine response and lead to the hypothesis that dopamine circuits could be altered in AN. Short-term follow-up studies have indicated that PE brain response in AN was inversely related to weight gain during intensive treatment. Interestingly, taste perception was negatively related to brain response. We are not aware of longitudinal studies (> 1 year) that have explored task-based brain response to predict long-term outcome. In this study, we wanted to test whether taste PE response at begin of treatment would be predictive of long-term weight loss or gain. Our primary hypothesis was that brain response in AN would inversely predict weight development over time. Second, we wanted to test whether higher sweet taste and pleasantness perception would be associated with higher long-term weight in AN.

Methods: We recruited 25 individuals who had previously participated in our brain imaging studies at begin of eating

disorder treatment. Participants completed the eating disorder examination questionnaire (EDE-Q) to measure the range and severity of eating disorder features. Participants also completed the Beck depression inventory-II, the Spielberger state anxiety questionnaire and recorded medication use. We retrieved age, body mass index (BMI, weight in kg/height in m2), sweetness and pleasantness perception (across 2%, 4%, 8%, 16%, 1molar sucrose solutions) and brain imaging results (dorsal anterior insula, ventral anterior insula, caudate head, orbitofrontal cortex, ventral striatum and nucleus accumbens) from those individuals. Non-normally distributed data were rank transformed before analysis. Correlation analyses tested associations between demographic, behavior and brain variables. We conducted linear multiple regression analyses to test whether brain or taste response predicted long-term BMI or BMI-change. To control for collinearity, the independent variables were standardized (Z-score) and analyzed in a factor analysis with varimax rotation before input into the regression models.

Results: A mean of 1790 (1030) days had passed since the brain scan. The AN group had a mean age of 23.9 (4.5) years, mean BMI of 19.8 (3.7), and a mean BMI change of 3.48 (3.4).

BMI at treatment begin did not significantly correlate with BMI or BMI change on long-term follow-up. Days between assessments was positively correlated with long-term BMI ($r = 0.426$, $p < 0.034$).

Long-term BMI was positively correlated with right ventral anterior insula brain activation ($r = 0.470$, $p < 0.018$, 95%CI 0.052-0.713).

Long-term BMI was also positively correlated with pleasantness for sucrose solution of 2% ($r = 0.416$, $p < 0.039$, 95%CI 0.143-0.637) and 16% ($r = 0.528$, $p < 0.007$, 95%CI 0.252-0.728) and with sweetness perception for 2% ($r = 0.567$, $p < 0.003$, 95%CI 0.210-0.781), 4% ($r = 0.398$, $p < 0.049$, 95%CI 0.029-0.628), 16% ($r = 534$, $p < 0.006$, 95%CI 0.290-0.752) and 1molar sucrose solution ($r = 0.518$, $p < 0.008$, 95%CI 0.264-0.711).

Change of BMI was positively correlated with sucrose solution pleasantness for 4% ($r = 0.415$, $p < 0.039$, 95%CI 0.154-0.666) and 16% ($r = 0.570$, $p < 0.003$, 95%CI 0.270-0.781), and with sweetness perception for 2% ($r = 0.533$, $p < 0.006$, 95%CI 0.211-0.749), 8% ($r = 0.455$, $p < 0.022$, 95%CI 0.065-0.736), 16% ($r = 0.552$, $p < 0.04$, 95%CI 0.265-0.777) and 1 molar ($r = 0.500$, $p < 0.011$, 95%CI 0.213-0.725).

Partial correlations controlling for days between assessments still showed significant correlations between long-term BMI and right ventral anterior insula brain activation ($p < 0.05$), and pleasantness for 2% ($p < 0.024$) and 16% ($p < 0.016$) sucrose solution, as well as BMI change and 16% ($p < 0.007$) and 1molar ($p < 0.029$) sucrose sweetness perception.

Multiple linear regression analyses for PE brain response predicting long-term BMI was significant (adjusted R square 0.557, $p < 0.019$) but the prediction of BMI change was not (adjusted R square 0.405, $p < 0.075$). Multiple linear regression analyses showed that sweetness and pleasantness predicted significantly long-term follow-up BMI (adjusted R square 0.534, $p < 0.012$) and BMI change (adjusted R square 0.558, $p < 0.009$). A model that combined taste perception and brain imaging response was not significant.

Conclusions: This study in individuals who were treated for AN indicates that long-term (greater than one year) follow-up BMI is independently predicted by PE brain response as well as taste perception for sucrose. Also, sweet and pleasantness taste perception also predicted BMI change over time. These data support the intriguing idea that long-term outcome can be predicted by brain activation but also measures for taste perception. This also raises the possibility that those measures are vulnerability factors for relapse. However, the mechanism for opposite association between short-term versus long-term weight gain is unclear. PE is coded by several dopamine receptors, and pharmacological challenge studies are needed to understand this brain response in AN further.

Keywords: Anorexia Nervosa, Clinical Outcome Prediction, Brain Imaging, fMRI, Taste, Perception

Disclosure: Nothing to disclose.

W64. Investigation of the Effects of Dasotraline in a Validated Rat Model of Binge-Eating Disorder

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Background: Dasotraline is a novel monoamine reuptake inhibitor. Dasotraline acts as a potent inhibitor of the human dopamine reuptake transporter (DAT; dopamine uptake IC50 = 3 nM) and noradrenaline (norepinephrine) transporter (NET; noradrenaline uptake IC50 = 4 nM), and a weaker inhibitor of the human serotonin (5-HT) transporter (SERT; serotonin uptake IC50 = 15 nM). Dasotraline has been shown in clinical trials to be effective in treating ADHD in adults (Koblan et al, 2015; Hopkins et al, 2016) and it is also currently in Phase 3 clinical development as a treatment for the management of binge-eating disorder (BED) in adults.

We have developed a model of binge-eating (BE) in which female rats not only exhibit aberrant bingeing, but also the behavioural traits of compulsivity and impulsivity that are core symptoms of BED in humans (Vickers et al, 2015, 2017; Heal et al, 2016). The effect of dasotraline on BE in this model was investigated.

Methods: BE was induced over 28-days in 40, singly-housed, female, Wistar rats (200 - 250 g; Charles River UK). They were maintained on a reverse phase light-dark (16/8 h) cycle. Rats had ad libitum access to standard, nutritionally balanced, laboratory chow and water, but BE rats were also given irregular access to powdered chocolate for 2 h at the start of the dark phase on some days. An empty pot was placed in the cages of the controls. BE was characterised by intense hyperphagia and consumption of an average of 162 kJ in 2 h (~50% of their daily intake). Dasotraline (2.25, 4.5 or 6.75 mg/kg), lisdexamfetamine (LDX; 0.3 or 1.0 mg/kg), d-amphetamine (0.5 or 1.0 mg/kg) or vehicle were dosed orally 2 h before the 2 h BE sessions. Pots of powdered chocolate and standard chow were available to the rats in the BE sessions. Doses are quoted as base except LDX which is reported as d-amphetamine base equivalents. Results are mean ± SEM.

Results: The vehicle-treated BE rats consumed 185 ± 6 kJ ($n = 29$) of chocolate in the 2 h BE test sessions. Dasotraline (2.25, 4.5 and 6.75 mg/kg po) dose-dependently reduced chocolate BE by -22.6% (143 ± 8 kJ, $n = 29$; $p < 0.001$), -56.3% (81 ± 6 kJ, $n = 28$; $p < 0.001$) and -80.5% (36 ± 12 kJ, $n = 8$; $p < 0.001$). LDX (0.3 or 1.0 mg/kg po) and d-amphetamine (0.5 or 1.0 mg/kg po) both reduced chocolate BE in a dose-related manner, ie -14.5% (158 ± 16 kJ, $n = 7$; $p = 0.094$), 41.8% (108 ± 15 kJ, $n = 7$; $p < 0.001$) and -22.3% (144 ± 13 kJ, $n = 7$; $p = 0.01$,), -50.0% (93 ± 22 kJ, $n = 7$; $p < 0.001$), respectively.

The vehicle-treated BE rats consumed 174 ± 6 kJ ($n = 29$) of standard chow over the 24 h period when there was a 2 h BE test session. The lowest dose of dasotraline had no effect on 24 h chow intake (172 ± 6 kJ), but the 2 higher doses reduced it by 20.3% (139 ± 5 kJ; $p < 0.001$) and 33.2% (116 ± 7 kJ; $p < 0.001$). Neither dose of LDX significantly reduced 24 h chow consumption (184 ± 9 kJ and 176 ± 7 kJ), d-Amphetamine had no effect on 24 h chow consumption at 0.5 mg/kg (196 ± 16 kJ), but increased it by 18.6% (207 ± 11 kJ; $p = 0.024$) at 1.0 mg/kg.

The mean bodyweight of the vehicle-treated BE rats was 305.8 ± 0.5 g ($n = 29$). When measured 24 h after dasotraline (2.25,

4.5 and 6.75 mg/kg po), the mean body weights of the rats were reduced by -1.0%, -1.7% and -3.5%, respectively (all $p < 0.001$). None of the doses of LDX or

d-amphetamine affected the rats' weight.

Conclusions: LDX is approved to treat BED in adults. These results confirm previous work showing that LDX decreases chocolate BE without affecting chow consumption (Vickers et al, 2015).

d-Amphetamine, the active metabolite of LDX, also decreased BE without affecting chow consumption at the lower dose. Dasotraline dose-dependently reduced chocolate BE. The lowest dose of dasotraline reduced chocolate bingeing by 22.6% without altering the consumption of standard chow. Although the 2 highest doses of dasotraline also reduced 24 h chow consumption, the effects on chow intake were much smaller, ie 20.3% vs 56.3% and 33.2% vs 80.5%, respectively. The results, therefore, demonstrate that dasotraline has a preferential effect to attenuate BE behaviour and support the hypothesis that dasotraline has the potential to be an effective treatment for BED.

Keywords: Binge Eating Disorder, Dasotraline, Lisdexamfetamine, Animal Models

Disclosure: Renasci Ltd, Board Member, Self

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W65. Methylphenidate Increases Effort-Based Decision Making in Adults With ADHD

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Background: Attention deficit/hyperactivity disorder (ADHD) is characterized by symptoms of inattention, hyperactivity, and impulsivity. These symptoms are thought to arise from hypoactive dopamine (DA) and/or norepinephrine (NE) systems. In particular, the inattention symptoms of ADHD have been associated with a reduction of DA synaptic markers (Volkow et al., 2011). A DA/NE reuptake inhibitor, methylphenidate, is a commonly prescribed medication for ADHD and produces modest improvements in working memory, reaction time variability, and vigilance (Pievsky and McGrath, 2018). While ADHD research has primarily focused on these neurocognitive impairments, the hypothesis that problems with attention are driven by DA-related changes in reinforcement sensitivity has been proposed, yet little empirical research has been conducted (Luman et al., 2010). DA function, in particular, has been related to motivated, effort-based decision making in rodent models of instrumental behavior. A paradigm of this behavior designed for human-subject research is the Effort Expenditure for Rewards Task (EEfRT), which measures the willingness to exert effort based on the magnitude and probability of reward receipt. Previously, d-amphetamine enhanced healthy adults' willingness to exert effort on this task (Wardle et al., 2011). In this ongoing study, we hypothesized ADHD symptoms in nonmedicated adults would be associated with a reduced willingness to exert effort, and that effort would be increased by methylphenidate.

Methods: Nonmedicated male and female adults with ($n = 22$) and without ($n = 17$) ADHD completed 2 study days, in which they received 40 mg methylphenidate or placebo in a double-blinded, counterbalanced design. During the EEfRT, participants make a series of choices between a low-effort option (i.e., making 30 button presses in 7 sec with the dominant-hand index finger) worth $1, and a high-effort option (i.e., making 100 button presses in 21 sec with the nondominant-hand pinky finger) worth between $1.24-$4.30. In addition, the probability of receiving the reward upon successful completion of the task varies from .12, .5 and .88. At the end of the task, a single trial is selected at random and the participant is paid the amount they received on that trial as a bonus.

Results: Overall, the number of high-effort choices increased in relation to the value and the probability of the high-effort reward (value x probability: $F(6,32) = 7.2$, $p < .001$). Both ADHD and non-ADHD participants made more high-effort choices on methylphenidate compared to placebo (drug: $F(1,37) = 9.2$, $p < .005$). Methylphenidate increased high-effort choices more in ADHD than non-ADHD participants (drug x group $F(1,37) = 4.7$, $p < .05$), although between-group differences were not significant. Furthermore, ADHD severity positively correlated with expected-value beta weights (i.e., how strongly expected value predicted choice behavior) during the placebo condition across all subjects (Spearman's $rho = .36$, $p < .05$). Additionally, men made more high-effort choices (between-group: $F(1,35) = 9.5$, $p < .005$), but sex did not interact with ADHD status.

Conclusions: The results suggest there are DA-related deficits in effort-based motivation among adults with ADHD, and methylphenidate may alleviate these deficits. Specifically, as ADHD severity increased across participants, expected value of the reward became a stronger predictor of the willingness to exert effort. These motivational deficits could potentially underlie or exacerbate different neurocognitive impairments, depending on the reinforcing value of the task performance.

Keywords: ADHD, Methylphenidate, Effort-Based Decision-Making Task

Disclosure: Nothing to disclose.

W66. Cortical Thickness Across the Lifespan in Relation to Psychopharmacological Treatment in OCD

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Background: Quantitative MRI studies in psychiatric disorders frequently find abnormal regional brain morphologic endpoints, such as cortical thickness (CT), but these endpoints might be influenced by treatment with psychotropic agents since participating patients are often medicated. Preclinical studies suggest that medication-related changes in dendritic spine density may contribute to CT effects and that these changes are common across most classes of psychotropic agents but may vary with for instance patient age. The present analysis sought to assess interaction effects of age and psychotropic medication on CT in obsessive-compulsive disorder (OCD), a common psychiatric condition with mostly lifelong pharmacological treatment.

Methods: We analyzed CT endpoint values from 33 centers participating in the worldwide ENIGMA-OCD consortium. Cross-sectional data were collected from 2176 (1111 male, 1065 female) subjects with DSM-IV OCD—including 1040 medicated (Med) and 1136 non-medicated (NMed) OCD patients-- and 2003 (995 male, 1008 female) healthy controls (HC). We divided the sample into 6 age brackets: Group 1 ages 6-13 (61 Med, 168 NMed, 242 HC); Group 2 ages 14-19 (185 Med, 168 NMed, 264 HC); Group 3 ages 20-29 (313 Med, 412 Normed, 847 HC); Group 4 ages 30-39 (272

Med, 273 NMed, 386 HC); Group 5 ages 40-49 (143 Med, 76 NMed, 169 HC); and Group 6 ages 50-65 (66 Med, 39 NMed, 95 HC). Using harmonized data processing and analysis pipelines, including rigorous quality control, at each center, T1-weighted whole-brain MRI acquired from each subject was parcellated into 34 bilateral cortical regions spanning the cerebrum, CT was calculated for each region using FreeSurfer 5.3. For each region, ANOVA was applied on the measure CT testing main effects of Medication (coded 0 for HC, 1 for NMed, 2 for Med) and of Group and the Group-by-Medication interaction with Bonferroni correction for multiple comparisons ($p < 0.0015$ threshold for significance).

Results: Med, NMed, and HC all showed significantly lower brain-wide CT with increasing age (main effect of Group typically $p < 0.0005$) in most cortical regions. The main effect of Medication (typically $p < 0.001$-0.0005) and the Group-by-Medication interaction (typically $p < 0.0005$) were also significant in many brain regions. Thereby, in Groups 1-2 (childhood, adolescence) Med subjects had higher CT than NMed subjects. In Groups 3-6 (adulthood), however, Med subjects had lower mean CT than NMed and HC; the biggest difference occurred for Group 4 (age 30-40). Results remained significant when sex, intracranial volume, and OCD symptom severity (Y-BOCS) were added to the model.

Conclusions: This is the first report to show that there are possible neurodevelopmental stage dependent effects of medication on CT. Specifically, medicated children aged 6-13 years (Group 1) exhibited the highest CT followed by a crossover in adolescence such that by young adulthood (Group 3, age 20-29 years) the Med group had lower CT than NMed or HC. Inferring from animal studies, this drug-by-age interaction might relate to variations in the density of dendrites and their sensitivity to psychotropic medication in childhood vs adulthood.

Keywords: Obsessive-Compulsive Disorder (OCD), MRI, Psychotropic Medications

Disclosure: Nothing to disclose.

W67. Testosterone, Lh Levels and Methylation Status in Men With Hypersexual Disorder

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Background: Hypersexual disorder as suggested to be included in the DSM-5 (Compulsive Sexual Behavior Disorder in ICD-11) integrates aspects of sexual desire deregulation, impulsivity and compulsivity. We have recently reported Hypothalamic pituitary adrenal (HPA-) axis dysregulation and related epigenetic changes in men with HD. However, it is unknown if hypersexual disorder is associated with altered gonadal activity and the function of hypothalamic gonadal (HPG) axis.

Methods: In this study we investigated testosterone and luteinizing hormone (LH) levels in 67 men with hypersexual disorder compared to 39 age matched healthy controls as well as epigenetic modifications in HPA- and HPG-axis coupled CpG-sites. Patients with HD as well as healthy controls were assessed using the Mini International Neuropsychiatric Interview and multiple psychometric scales m of hypersexuality. Basal morning plasma levels of testosterone, Sex Hormone-Binding Globulin (SHBG), and LH were assessed using the an electrochemiluminescence immunoassay. The genome-wide methylation pattern of over 850 K CpG-sites was measured in whole blood using the Illumina Infinium Methylation EPIC BeadChip and was pre-processed according to standard protocols and adjusted for white blood cell type heterogeneity. CpG-sites located within 2000 bp of the transcriptional start site of the following HPA and HPG axis coupled genes were included: Corticotropin releasing hormone (CRH), corticotropin releasing hormone binding protein (CRHBP), corticotropin releasing hormone receptor 1 (CRHR1), corticotropin releasing hormone receptor 2 (CRHR2), FKBP5, the glucocorticoid receptor (NR3C1), Gonadotropin releasing hormone receptor (GNRHR), luteinizing hormone/choriogonadotropin receptor (LHCGR), Estrogen receptor α (ESR1) and β (ESR2), progesterone receptor (PGR), androgen receptor (AR), sex hormone binding globulin (SHBG), G protein-coupled estrogen receptor (GPER), aromatase estrogen synthetase (CYP19A1), 5 α-reductase (SRD5A1), oxytocin receptor (OXTR), kisspeptin (KISS1) and kisspeptin receptor (KISS1R). Student t-test and Kruskal-Wallis' test were used to investigate group differences in continuous variables. We performed multiple linear regression models of methylation M-values to plasma testosterone levels adjusting for plasma levels of SHBG and LH as well as methylation M-values to plasma LH levels adjusting for plasma levels of testosterone respectively.

Results: LH plasma levels were significantly higher in male patients with HD (Mean ± SD) (4.13 ± 1.57) compared to healthy volunteers (Mean ± SD) (3.57 ± 1.47) ($P = 0.035$). No significant differences in plasma testosterone and SHBG levels were found between hypersexual men (Mean ± SD) (15.09 ± 4.49); (32.59 ± 11.29) and healthy controls (Mean ± SD) (14.34 ± 4.29) (35.15 ± 13.79). 221 individual CpG-sites were tested. For testosterone plasma levels, twelve were nominally significant ($p < 0.05$), (genes CRH, CRHBP, CRHR2, ESR1, ESR2, GPER, KISS1R, OXTR, SHBG) and twenty for LH plasma levels (genes CRHR1, CRHR2, ESR2, GPER, KISS1R, OXTR, SHBG). No individual CpG site was significant after multiple testing corrections with the FDR-method.

Conclusions: Our results show preliminary evidence of dysregulation of the HPG axis with increased LH plasma levels in hypersexual men compared to healthy volunteers, while we do not observe significant epigenetic changes in HPA or HPG axis related genes associated to LH and testosterone levels in men with hypersexual disorder.

Keywords: Hypersexual Disorder, Testosterone, Epigenetics, HPA axis

Disclosure: Nothing to disclose.

W68. DHEA and DHEAS Levels in Combat Veterans With or Without a History of Suicide Attempt

Abstract not included.

W69. Norepinephrine Reuptake Inhibition Enhances the Control of Impulsivity by Activating D1-Like Receptors in the Infralimbic Cortex

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Background: Higher impulsivity is a risk factor for criminal involvement, substance abuse, and suicide. However, only a few drugs are clinically available for the treatment of deficient impulse control. We recently proposed a strategy for identifying potential drugs to treat such disorders by investigating clinically available drugs that increase extracellular dopamine levels in the medial prefrontal cortex and stimulate dopamine D1-like receptors without increasing extracellular dopamine levels in the ventral striatum (Ohmura et al. 2012, J Pharmacol Sci). This proposal is based on previous studies showing that impulsive behavior is inhibited by dopaminergic functions in the medial prefrontal cortex and promoted by those in the ventral striatum and on a study demonstrating that dopamine D1-like receptors in the infralimbic cortex play a pivotal role in the control of impulsive behavior. As previously suggested (Ohmura et al., 2012),

norepinephrine reuptake inhibitors might meet these criteria because the norepinephrine transporter sometimes transports dopamine in brain regions in which the dopamine transporter is sparsely expressed, such as the medial prefrontal cortex. Thus, our goal was to determine whether this strategy is promising.

Methods: We examined the effects of duloxetine, a serotonin-norepinephrine reuptake inhibitor that might meet these criteria, on impulsive action in adult male Wistar/ST rats using a 3-choice serial reaction time task. This task is a simplified version of the 5-choice serial reaction time task, and can assess impulsivity, motor function, attentional function, and motivation/appetite simultaneously. We injected duloxetine (0, 0.3, 1.0, and 3.0 mg/kg) intraperitoneally into rats 60 min before the 3-choice serial reaction time task testing session. Moreover, the effects of anti-impulsive dose of duloxetine on extracellular dopamine levels in the medial prefrontal cortex and nucleus accumbens, a part of the ventral striatum, were evaluated using in vivo microdialysis. Furthermore, we examined whether the anti-impulsive effects of duloxetine could be blocked by microinjections of a D1-like receptor antagonist (SCH23390, 3.0 ng/side) into the infralimbic cortex. In addition, we repeated the same experiment, but using atomoxetine (1.0 mg/kg, i.p.), a norepinephrine reuptake inhibitor and an established anti-impulsive drug, to confirm whether the same mechanisms underlie the anti-impulsive effects of these drugs.

Results: Systemic administration of duloxetine dose dependently reduced impulsive actions without affecting other parameters such as motor function, attentional function, or motivation/appetite. Moreover, the anti-impulsive dose of duloxetine (3.0 mg/kg) increased extracellular dopamine levels in the medial prefrontal cortex but not in the nucleus accumbens. Microinjection of a selective D1-like receptor antagonist into the infralimbic cortex blocked the suppression of impulsive action by duloxetine. In addition, consistent with previous studies, systemic administration of atomoxetine alone reduced impulsive action, while the microinjection blocked the suppression of impulsive action by atomoxetine.

Conclusions: Our results suggest that norepinephrine reuptake inhibitors, duloxetine and atomoxetine, likely enhance the control of impulsivity in rats by increasing dopamine levels in the medial prefrontal cortex and stimulating the dopamine D1-like receptors in the infralimbic cortex. These results are consistent with our previous suggestion (Ohmura et al., 2012), indicating that our hypothesis could be used as a guide to developing anti-impulsivity drugs.

Keywords: Impulsivity, Serotonin and Norepinephrine Reuptake Inhibitor, Microdialysis, Dopamine, Medial Prefrontal Cortex

Disclosure: Nothing to disclose.

W70. The Medial Septum Enhances Reversal Learning via Actions on Ventral Tegmental Area and Substantia Nigra Dopamine Neurons

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Background: The medial septum (MS), a sub region of the basal forebrain, has been shown to be involved in learning and memory processes, specifically response inhibition. For example, lesion of the MS increases perseverative responding and inhibits fear extinction. Although the MS is known to drive theta rhythmicity in the hippocampus, the actual mechanism by which the MS affects learning and memory is not well-understood. However, it was recently demonstrated that MS activation increases dopamine (DA) population activity in the ventral tegmental area (VTA) and decreases DA activity in the substantia nigra pars compacta (SNc). Both effects were mediated via a pathway that involves the ventral subiculum (vSub) and ventral pallidum. Therefore, one potential mechanism is that the MS aids in response inhibition via its regulation of midbrain DA activity, possibly by attenuating SNc-driven habit-related responding in favor of VTA-driven goal directed responding. However, this hypothesis has not been tested.

Methods: This hypothesis was tested by infusing a DREADD-containing (hM3Dq) or control virus into the MS of Sprague Dawley rats. Eight to twelve weeks later, the effect of MS activation on midbrain DA activity and T-maze reversal learning was determined following systemic and intracranial (vSub) injection of CNO, both with and without a co-injection of the D1 antagonist SCH23390.

Results: DREADD activation of the MS via systemic CNO injection resulted in a 32% reduction in the number of trials required to perform a reversal in the T-maze task and reduced the number of perseverative errors by 37% compared to the control groups. Infusion of CNO directly onto MS terminals in the vSub increased (78%) the number of spontaneously active DA neurons in the VTA, and decreased (31%) the number of active DA neurons in the SNc, similar to what was shown previously via NMDA activation of the MS. Infusion of CNO directly onto MS terminals in the vSub also produced a similar enhancement in T-maze performance, suggesting that both the effect on midbrain DA activity and T-maze performance were mediated via the direct projection from MS to vSub. Finally, co-injection of the D1 antagonist SCH23390 completely prevented the enhancement in reversal learning performance seen in the DREADD/CNO rats, suggesting the MS's effect on DA transmission is necessary for its enhancement of reversal learning.

Conclusions: These data demonstrate that DREADD activation of the MS enhances reversal learning and reduces perseverative responding. Furthermore, it indicates that the manner by which the MS exerts its effect on reversal learning is, at least in part, due to its effect on DA transmission, a mechanism that had not been known previously. This suggests that the MS, via its regulation of the DA system, may be critical for response inhibition and cognitive flexibility, two functions that are central to higher order cognitive processing and are disrupted in several psychological disorders. As such, manipulation of this pathway may prove to be beneficial in treating cognitive dysfunction in a broad range of diseases, including schizophrenia and addiction.

Keywords: Medial Septum, Dopamine Circuitry, Reversal Learning, Ventral Hippocampus, Electrophysiology

Disclosure: Nothing to disclose.

W71. Exploring the Role of the Habenular-Interpeduncular Circuit in Affective States in Diabetes

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Background: Previous work in the Kenny lab has linked the Habenula-Interpeduncular circuit (Hb-IPN) to central regulation of blood glucose levels via cells expressing nicotinic cholinergic receptors (nAChRs) in response to nicotine. My own work has demonstrated that nitric oxide synthetase 1 (NOS1) in Chrna5-expressing cells in the IPN is necessary for preference for nicotine and is upregulated by chronic nicotine exposure. Our data suggests that nitric oxide inhibits glutamate release from the Hb, thereby reducing the strength of aversion mediated by the Hb

and leading to the development of tolerance. Epidemiological data demonstrates that diabetics are twice as likely as healthy individuals to suffer from depression and twice as likely to smoke. Animals models confirm that diabetic states increase an animal's vulnerability to depression-like behaviors. Further, the Hb complex has been implicated in depression and addiction as a regulator of serotonergic and dopaminergic tone. It is well-established that cholinergic and nitrergic signaling is disrupted in brains of diabetics or streptozotocin (STZ)-treated animals, and that both NOS1 and the habenula have been implicated in depression, however, to date no one has examined the Hb-IPN in diabetics. Here we describe studies that examine the molecular response of specific vulnerable cell types to hyperglycemia as well as the contribution of dysregulated nitrergic signaling in the IPN to affective states in diabetes.

Methods: We are using several animal models of diabetes to characterize changes in the Hb-IPN in response to hyperglycemia at the molecular, cellular and behavioral level. All experimental protocols were approved by the Institutional Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Wild type C57Bl6J mice were injected i.p. with control solution (n = 15) or STZ (n = 15) to induce diabetes. Hyperglycemia was confirmed by blood glucose measurements from tail vein. Animals subsequently underwent behavioral battery to assess baseline locomotion, anxiety, social interaction and motivation. Following behavioral assays, brain and pancreas was collected for histology for NOS1. A second cohort of wild type C57Bl6J mice were injected with control virus (n = 10) or virus expressing shRNA against NOS1 (n = 10) in the IPN. Two weeks after viral injection, animals underwent the same behavioral battery and blood glucose was measured. To determine cell-type specific changes in gene expression induced by diabetes, ChAT-Cre and VGAT-Cre were crossed to Rosa26-EGFPL10a mice. Double positive mice were injected i.p. with control solution (n = 5 mice per sample, performed in triplicate) or STZ (n = 5 mice per sample, performed in triplicate) to induce diabetes. Hyperglycemia was confirmed by blood glucose measurements from tail vein. Brain regions were microdissected and translating ribosomal affinity purification (TRAP) performed, followed by qPCR and RNA-Seq.

Results: Studies are currently underway. We have preliminary data demonstrating that chemogenetic activation of the IPN is sufficient to increase blood glucose acutely, confirming a central role of this circuit in blood sugar regulation. TRAP data from ChAT Hb cells and GABAergic IPN cells confirm presence of genes linked to diabetes in multiple GWAS: Tcf7l2 and Chrm3, respectively.

Conclusions: Depression is twice as likely to occur in diabetics as in healthy individuals. Given that the prevalence of diabetes is reaching epidemic proportions world-wide (422 million in 2014) and that depression is the leading cause of disability, it is important to address adequate treatment options in this population. Our work aims to understand the molecular mechanisms by which hyperglycemia contributes to neuronal dysfunction and resulting depressed mood, with the ultimate goal of discovering pathways that can be targeted for more effective treatment.

Keywords: Diabetes, Affective Disorders, Neuronal Nitric Oxide Synthase, Cholinergic System

Disclosure: Nothing to disclose.

W72. SXC-2023: Characterization of a Novel Activator of the Cystine-Glutamate Antiporter and Potential Therapeutic for CNS Disorders

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Background: Impaired cortical control over impulses and urges is a hallmark feature of many disorders of the central nervous system (CNS), including trichotillomania, excoriation [skin picking] disorder, obsessive compulsive disorder, and various addictions. Altered glutamatergic neurotransmission and/or oxidative homeostasis are purported to underlie the pathological progression of these impulse control disorders (ICDs). The cystine-glutamate antiporter (also known as System xc- or Sxc) is expressed within key areas of the brain (i.e., the inhibitory cortico-striatal pathway) where it can modulate glutamate signaling and increase the synthesis of the body's primary antioxidant, glutathione. SXC-2023 is a small molecule activator of System xc- and is under development for the treatment of trichotillomania, a neuropsychiatric disorder defined by recurrent, hair pulling behaviors.

Methods: Standard in vivo CNS paradigms including elevated plus maze (EPM; n = 7-10 male SD rats per dose group), which is used to measure anxiety (a symptom of many psychiatric disorders and is an indicator of CNS penetration), and pre-pulse inhibition (PPI; n = 7-26), which tests behaviors dependent on cortical glutamatergic transmission, were performed to measure the nonclinical activity of SXC-2023 (3 to 30 mg/kg, PO). Also, in the PPI paradigm, SXC-2023 (10 mg/kg) was evaluated in rats where a germline mutation of Slc7a11 eliminated System xc- activity (n = 10-12 per group). Behavioral measures were time spent on the open arm of the EPM and startle behaviors in PPI induced by the N-methyl-D-aspartate receptor antagonist MK-801 (0.1 mg/kg, SC).

Results: Oral administration of SXC-2023 dose-dependently increased the time spent in the open arm of the elevated plus maze [$F(3,80) = 3.47$, $p < .05$] and significantly ameliorated MK-801-induced deficits in PPI [$F(1, 170) = 8.92$, $p < .001$]. Additionally, the effects of SXC-2023 in PPI were abolished in System xc- deficient rats [$F(1, 32 = 2.96$, $p > .05$]. Based on the strength of this nonclinical profile, coupled with the absence of any significant safety, toxicity and/or tolerability concerns following repeated (28-day) administration at high doses (e.g., 1000 mg/kg/day in rats), SXC-2023 has entered clinical development.

Conclusions: These results suggest that SXC-2023 reverses behavioral deficits associated with glutamatergic dysfunction and heightened levels of oxidative stress, both of which are implicated in the pathophysiology of ICDs. Moreover, these findings suggest that SXC-2023, by activating System xc-, may represent a safe, well-tolerated and promising approach for the treatment of impulse control disorders such as trichotillomania.

Keywords: Disorders of Glutamate, Oxidative Stress, Trichotillomania

Disclosure: Nothing to disclose.

W73. Prediction of Suicidal Attempt Using Optum Integrated Claims-Clinical Dataset

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Background: The ability to predict suicidal attempt will allow timely intervention to prevent the suicide death. Predictive modeling was used to identify patients at risk for suicidal attempts using Optum Integrated Claims-Clinical dataset.

Methods: Suicide attempt was defined using ICD codes as proposed by Barak-Corren et al. Both ICD-9 and the corresponding ICD-10 codes were used. Suicidal attempt events between 2007-07-01 and 2017-06-30 were included to define the cases (n = 177,212) and the last suicidal attempt date was used as an index date. Similarly, matched controls without lifetime suicidal attempt

(n = 177,212) were drawn from the same period except the last clinical encounter date was used as the index date. Predictors were demographic variables, lifetime indicators of comorbidity, healthcare service utilization or similar indicator variables 12 or 24 months before the index date. The overall samples were divided into training (80%, n = 284,340) and independent test samples (20%, n = 70,084). Within training data, nested cross-validation was performed to build an ensemble of extreme gradient boosting (XGB) predictive models which were tested on the independent test samples.

Results: Applying the XGB model to independent test data (setup identical to training data) resulted in an area under the receiver operating characteristic curve (ROC AUC) of 89% and model balanced accuracy of 81%, sensitivity of 81%, and specificity of 81%.

Conclusions: Risk models can be integrated to electronic medical record (EMR) to identify at-risk subjects to enhance clinical care and to guide the delivery of preemptive interventions.

Keywords: Suicide Prediction, Machine Learning, Predictive Models, Electronic Medical Record

Disclosure: Johnson and Johnson, Employee

W74. Irritability in Huntington's Disease: A Phase 2 Exploratory Clinical Trial With a Novel Vasopressin 1a Antagonist, SRX246

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Background: Irritability, anger, and aggression are common in Huntington's Disease (HD) patients. These symptoms are highly distressing aspects of the disease, adversely impact daily life, and often result in institutionalization. Effective treatments are lacking and well-validated scales for measuring changes in these symptoms are not available. This Phase II clinical trial in HD patients (n = 106), Safety and Tolerability of SRX246 In Irritable/Aggressive Subjects with Huntington's Disease (STAIR; NCT02507284), rigorously evaluates the tolerability of a new drug, SRX246; provides additional safety data; and explores rating scales for the assessment of changes in these symptoms. The test drug, SRX246, is a first-in-class vasopressin 1a receptor antagonist. It exhibits high affinity and selectivity for its target, has a strong safety profile in healthy volunteers and other clinical trials, and excellent pharmacokinetics. Preclinical pharmacology and an experimental medicine fMRI study showed that SRX246 has CNS effects after oral administration and modulates brain circuits involved in responses to stimuli that elicit aggression/fear. In a completed Phase 2 Exploratory trial for the treatment of Intermittent Explosive Disorder, SRX246 was well tolerated, no serious adverse events were reported, and exploratory analyses revealed statistically significant differences favoring SRX246 in key clinical outcome measures. These findings suggested that SRX246 might have beneficial effects on the irritability/aggression seen in HD patients.

Methods: STAIR is a 3 arm, multicenter, randomized, placebo-controlled, double-blind, 12-week dose escalation study (22 sites in the NINDS NeuroNext network, total n = 106). Following eligibility determination, female and male subjects were randomized to receive placebo or escalate from 80 mg (two weeks) to 120 mg, up to a maximum dose 160 mg twice daily of SRX246 for 12 weeks. Subjects have a study partner to assist with visits, taking study medication, and providing feedback about the subject's mood and behavior. Visits are either "in-person" or by "telephone". An eDiary (smart phone or tablet) prompts subjects to take their capsules. The subject and study partner are also asked to answer daily questions about irritability and behavior (also recorded in the eDiary). Visits occur at week 0 (baseline), 2, 4, 6, 8, 10, and 12.

The primary objective is to evaluate the tolerability of SRX246. This will be met through an equivalence test of the proportion of completers among the placebo group and each of the treatment groups. The study is powered to 80% with alpha = 0.025. The secondary objective is to evaluate the safety of SRX246. The objective will be met through an equivalence test of the proportion of subjects with AEs or SAEs among the placebo group and each of the treatment groups. Exploratory analyses will determine changes in irritability, anger, and aggression on various rating scales, including the Aberrant Behavior Checklist, Irritability Subscale; Cohen-Mansfield Aggression Inventory; Clinical Global Impression – Improvement; Problem Behaviors Assessment – short form; Irritability Scale; Caregiver Burden Questionnaire; Huntington's Disease Quality of Life Measure, and eDiary Responses. The objective is to obtain critical data that can be used to plan future Phase 2b or 3 clinical trials because there currently are no validated scales for the assessment of these symptoms in HD patients.

Results: As of August 6, 2018, 125 subjects were screened, 106 were randomized (55 female, 51 male, mean age = 50.6 + /- 12 years), and 93 have completed the protocol. The last patient was randomized in early June and the last visit is September 7, 2018. Compliance has been excellent and while we are blinded, the AE profile and tolerability are consistent with other trials that tested SRX246 that showed very good safety and tolerability. To date, a total of 186 AEs have been reported (in 78 study participants) after receiving study drug or placebo. The most commonly reported are "Nausea" (8%), "Fatigue" (6%), "Upper Respiratory Tract Infection" (6%), "Fall" (5%), and "Somnolence" (5%). Of the 186 AEs, nine (5%) have been classified as SAEs to date – in 9 subjects. Of these, none have been classified as both related to study treatment and unexpected.

Conclusions: The tolerability and safety profiles, which to date are blinded data, are consistent with prior results obtained with SRX246 in a Phase 1 multiple ascending dose trial and an experimental medicine study that showed good tolerability and safety. The exploratory analyses are expected to yield critical data that can be used to plan future Phase 2b or 3 clinical trials.

Keywords: Huntington's Disease, Irritability, Aggression, Vasopressin 1a Receptor Antagonist, CNS Clinical Trials

Disclosure: Azevan Pharmaceuticals, Inc, Stock / Equity, Consultant, Board Member

W75. Topology of Prefrontal Fibers in the Forceps Minor: Location Matters

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Background: The forceps minor is the part of the corpus callosum (CC) that carries prefrontal cortical (PFC) fibers. It is a particularly thick part at the genu of the CC, as it carries fibers not only from the adjacent regions to the CC but also PFC fibers rostral to the CC. Changes in the forceps minor white matter integrity have been demonstrated across several neuropsychiatric diseases, including, but not limited to obsessive compulsive disorder, autism, schizophrenia, and depression. Moreover, damage of forceps minor fibers correlates with the severity and/or extent of related symptoms. In these studies, the forceps minor is treated as one entity, the region that carries PFC fibers. However, due to: 1. the

high number of PFC areas that contribute fibers to it, 2. its thickness, and 3. its links to disease, we asked whether the forceps minor could be further segmented into regions that carried fibers from specific PFC regions. The goal of this study was therefore to determine the topology of PFC fibers in the forceps minor to better pinpoint connections that are abnormal in disease. We first used tract tracing in non-human primates (NHPs) to clearly define the topology of PFC fibers in the forceps minor. To help transition these results to the human brain, we next compared the tracing results with tractography using diffusion magnetic resonance imaging (dMRI) in NHP. Using this information as a guide, we analyzed human dMRI data. Our findings suggest a highly organized topological map of PFC fibers in the forceps minor consistent across NHPs and humans.

Methods: Anterograde or bidirectional tracers were injected into 36 sites evenly distributed in the following regions: frontal pole (FP), ventromedial PFC (vmPFC), orbitofrontal cortex (OFC), ACC, ventrolateral PFC (vlPFC), dorsolateral PFC (dlPFC), dorsomedial PFC (dmPFC). Fiber bundles traveling through the corpus callosum were outlined under darkfield microscopy in the software Neurolucida (MBF Bioscience) and integrated into a 3D model via IMOD. Diffusion magnetic resonance imaging (dMRI) data of 15 animals and 35 humans were used to reconstruct the callosal pathways with tractography and compare with the tracing result.

Results: In general, fibers in the most ventral part of the forceps minor connect regions of the vmPFC; those in the central part of the bundle connect OFC, vlPFC and ACC regions; fibers in the most dorsal part connect regions of the dorsal PFC. In addition to this general organization, the PFC fibers follow three topological rules. The first rule applies to PFC regions in the dorsal-ventral direction: Axons from dorsal PFC regions occupy a dorsal portion of the forceps minor, while those from ventral regions are located ventrally. The second rule applies to PFC regions in the lateral-medial direction: Fibers from lateral PFC regions occupy a dorsal portion of the forceps minor, while those from medial regions are located ventrally. This rule is secondary to the first rule, i.e. the position of fibers in the forceps minor is primarily determined by the dorsal-ventral position of its originating region. For regions at similar dorsal-ventral levels, their fibers follow the second rule. The third rule applies to PFC regions in a rotated rostral-caudal direction: If one follows the longitudinal axis of the genu, fibers located in the same callosal section originate from a set of cortical sites aligning in the radial direction. Such radial arrangement forms a rotated rostral-causal pattern centering at the genu. The same organizational rules are followed by streamlines generated from diffusion tractography, both in NHP and in human.

Conclusions: The PFC fibers passing through the forceps minor follow three organizational rules: 1) dorsal-dorsal & ventral-ventral; 2) lateral-dorsal & medial-ventral, and 3) rotated rostral-rostral & caudal-caudal. Segmentation based on these rules shows how abnormalities at particular sites throughout the forceps minor will likely impact different PFC areas in disease. This segmentation helps better interpret the disrupted pathways and functions associated with FA changes in patient dMRI.

Keywords: Forceps Minor, PFC, Tract Tracing, Diffusion Weighted Imaging, Pathway Analysis

Disclosure: Nothing to disclose.

W76. Modeling Sex Differences in the Immune Response to Major Depressive Disorder

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Background: There is a bi-directional relationship between the immune system and major depressive disorder (MDD). Autoimmune diseases and MDD are both more common in women than men. Little is known about mechanisms contributing to the higher incidence of inflammatory and stress-related illness in females. Here, we compare sex differences in cytokine profiles for humans with MDD to different stress-based mouse models.

Methods: Plasma was sampled from pre-menopausal women and age matched men with a diagnosis of MDD or healthy controls. In mice, male and female subjects were given a 6-day course of variable stress (acute stress) or exposed to 28-day variable stress or social defeat stress (chronic stress). Cytokine protein levels were detected using multiplex enzyme-linked immunosorbent assays. Sex differences were examined by group effects followed by within sex analysis and by correlation to quick inventory of depressive symptomology (QIDS) scores or behavioral measures.

Results: In humans, women had a more exaggerated immune response to MDD even when cytokines were regulated in the same direction. When data from men and women were analyzed separately, 13 cytokines were significantly regulated by depression in women and only 1 was significantly regulated in men. In depressed patients we found that IL-17a and MCP-1 significantly correlated with QIDS scores. We also observed greater immune dysregulation of female mice following 6-day variable stress and social defeat stress but not 28-day variable stress. Social defeat stress produced more overlap with cytokines altered by MDD than variable stress at either timepoint in both sexes. Some of the cytokines that were significantly upregulated in women with MDD and social defeat stress were significantly down regulated following acute stress and may represent a mechanism that leads to immune dysregulation following chronic stress or multiple bouts of stress/depression.

Conclusions: Women with MDD have greater dysregulation of pro-inflammatory cytokines then men. We can model the pattern of greater cytokine dysregulation in female mice across different stress paradigms. Social defeat stress represents an immune model of treatment resistant depression. Variable stress (6 days) may model cytokine changes occurring during the first episode of depression.

Keywords: Depression Inflammation Cytokine, Stress, Sex Differences

Disclosure: Nothing to disclose.

W77. Targeting Inflammation and Synaptic Maladaptation for the Treatment of Depression

Abstract not included.

W78. Cross-Species Epigenetic Signature in Ovarian Hormone Sensitivity

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Background: Sex hormones and their neurosteroid metabolites contribute to the establishment of sex differences as well as the regulation of affective state. In many women, natural fluctuations in circulating ovarian steroids across the menstrual cycle are associated with negative emotions. We investigated an animal model of genetic sensitivity to the ovarian hormone estradiol (E2), to identify genes conserved within females across species, that may also serve a greater biological purpose, such as adaptation to

environmental challenges. In rodents, E2 surge during the estrous cycle induces brain-derived neurotrophic factor (BDNF) mRNA and protein and increases the activation of the BDNF tyrosine kinase receptor, TrkB, in the hippocampus, suggesting converging functional actions of ovarian hormones and BDNF in the brain. Mice with a single nucleotide polymorphism of the human BDNF gene (Val66Met; rs6265), which results in an amino acid change from a valine to a methionine at position 66, show a negative behavioral response to ovarian hormone fluctuations, resembling that of women with premenstrual dysphoric disorder (PMDD) to estrogens. Using a whole-genome RNA-sequencing (RNA-seq) analysis, encompassing mouse and human studies, we report that E2 affects the epigenome in a mouse model carrying the BDNF Met variant, in a way that recapitulates the hallmarks of PMDD.

Methods: Ovariectomized mice heterozygous for the BDNF Met allele (Het-Met) and their matched wild type (WT) mice were administered E2 or vehicle in drinking water for six weeks. The ventral hippocampus was dissected and processed for RNA-seq. Three biological replicates were used per experimental group, comprising of RNA pooled from two animals each. Women between the ages of 18 and 48 years were included in the clinical study; all were medication-free, had regular menstrual cycles, medically well and not pregnant. Lymphoblastoid cell lines (LCLs), created from control women and women with PMDD, were treated or not with estradiol, and processed for RNA-seq. To compare the human and mouse genomes, a DESeq2 analysis pipeline through R was used to quantify both species' raw reads and obtain p-values ($p < 0.05$, Benjamini-Hochberg false discovery rate), and fold change (> 1.3).

Results: Through a comparative whole-genome RNA-seq analysis between mouse ventral hippocampus and LCLs, we identified a remarkable number of orthologues that were induced by E2 in both species. A GO analysis of commonly regulated genes revealed, among the top 10 enriched pathways, two major epigenetic clusters, namely, transcription and covalent chromatin modification. Common epigenetic genes were entered into GeneMANIA, a software that computes connection density and strength of the input genes and identifies genes that are strongly correlated to the interaction network. The epigenetic interactome that overlapped women and mouse included MEF2C, HDAC1, USP47, PPARD, ARID1A, HDAC3, SMARCB1, PRKD2, SMARCC2, NCOR2, HDAC11, PLAA, SUPT6H, and PITRM1, as well as the ESC/E(Z) complex genes SUZ12, EZH2, HDAC2, and JARID2. Interestingly, ESC/E(Z) complex, an effector of response to ovarian steroids, has been recently associated with PMDD.

Conclusions: E2 add-back induced intrinsic, common epigenetic modifiers in the ventral hippocampus of ovariectomized Het-Met mice and LCLs of PMDD women that transcended species and cell types. In particular, BDNF Met genotype intersected the epigenome of women with PMDD, showing a cluster of epigenetic modifiers by which ovarian steroids may produce negative behavioral effects. Animal models of ovarian hormone sensitivity can help shed light on epigenetic markers conserved across species relevant for novel diagnostic and therapeutic interventions.

Keywords: BDNF Val66Met, Premenstrual Dysphoric Disorder, Epigenetics, Cross species, RNA Sequencing

Disclosure: Nothing to disclose.

W79. Enkephalin-Expressing Ventral Pallidal Neurons Control Aversive Learning

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Background: The ventral pallidum (VP) is a critical component of the basal ganglia neurocircuitry and has been implicated in controlling hedonic responses to rewards. However, its possible role in controlling Pavlovian conditioning of cues associated with rewarding or aversive outcomes is unclear. Our group has previously demonstrated that nucleus accumbens (NAC) dopamine D1- or D2-receptor-expressing neurons are known to control reward and aversive learning, respectively (Hikida et al, 2010, Neuron). While classically it was thought that only NAc D2-neurons project to the VP, recent evidence has shown that a subpopulation of D1-neurons also projects to the VP, suggesting that VP neurons may play a role in either/both types of learning (Kupchik et al, 2015, Nature Neuroscience).

Methods: We used a Tet-Tag AAV virus system, in which designer receptors exclusively activated by designer drugs (DREADDs) were expressed in a population of VP neurons containing the peptide enkephalin, to investigate the possible role of the VP in reward and aversive learning. We tested reward learning measuring pavlovian approach behavior in an autoshaping task in touchscreen operant chambers (Macpherson & Hikida, 2018, Front Neurosci). Over the course of 6 daily sessions, a food reward was paired with the presentation of one conditioned stimulus (CS +), but not the presentation of another conditioned stimulus in a different location (CS-). During these conditioning sessions, we measured approaches to the CS + or food magazine during CS + presentation as a measure of sign-tracking and goal-tracking, respectively. We also examined a latency to enter the foot-shock-associated chamber when tested 24 h later in the one-trial inhibitory avoidance task (Hikida et al, 2010, Neuron).

Results: During acquisition of an autoshaping task, hM3Dq DREADDs were activated by administration of CNO, leading to increased activity in enkephalin-expressing VP neurons. Both CNO-treated and saline-treated (control) mice showed an equal ability to acquire the task, as indicated by an increase in Pavlovian approach behavior to a reward-associated cue over the course of 6 daily sessions. Whereas, in a passive avoidance task, administration of CNO during conditioning of an aversive foot-shock upon entering a dark chamber resulted in a decreased latency, in comparison to saline-treated controls, to enter the foot-shock-associated chamber when tested 24 h later.

Conclusions: These findings indicate that activity in enkephalin-expressing VP neurons disrupts aversive, but does not alter appetitive, Pavlovian conditioning. Thus, decreased activity in enkephalin-expressing VP neurons appears to be necessary for aversive learning, which supports previous evidence from our group that neurotransmission blocking in NAc D2-neurons, likely leading to disinhibition of downstream VP neurons, similarly inhibits passive avoidance learning.

Keywords: Dopamine Receptors, Basal Ganglia, Associative Learning

Disclosure: Nothing to disclose.

W80. Connective Tissue Growth Factor (CTGF) is Pro-Depressant: Findings From Human and Animal Studies

Abstract not included.

W81. Altered Network Activity in a Human 3D Cortical Sphere Model of Psychiatric Disorders

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Background: Induced pluripotent stem cells (iPSCs) are a powerful tool to dissect the biology of human cell types that are not easily amenable to study such as neurons and other cell types of the central nervous system. IPSC-derived neuronal cultures from patients provide the opportunity to uncover new disease mechanisms and phenotypes that can be used for drug discovery. However, robust, high-throughput platforms for measuring neuronal activity in human iPSC-derived neuronal cultures has been lacking. Synchronized calcium oscillations caused by bursts of synaptic activity are a feature of developing synaptic networks. Here we highlight a platform for measuring spontaneous calcium oscillations from 3D cultures of human neurons and astrocytes. 3D spheres display highly synchronized activity that can be measured by the kinetic high-throughput platform fluorometric imaging plate reader (FLIPR). Further, we utilized this platform for disease modeling of psychiatric disorders caused by a frameshift mutation in disrupted in schizophrenia 1 (DISC1). This mutation cosegregated in a family with major psychiatric disorders and was shown to cause synaptic phenotypes in iPSC-derived neurons including decreased synapse number and synaptic vesicle release deficits. We generated 3D spheres from isogenic iPSCs that contain wild-type or mutant DISC1 protein and analyzed their activity over time.

Methods: 3D cortical spheres were generated from iPSCs with a frameshift mutation in DISC1 and an isogenic control. IPSCs were first directed to forebrain neural progenitor cells (NPCs) and 3D cultures were generated from the NPCs by plating cells in low-attachment 384 well plates. Spontaneous network activity was monitored weekly over a 12-week time-period using calcium dye and FLIPR. For each genotype (control and DISC1) 12 spheres were measured per timepoint and each timepoint was repeated in 3 independent differentiations. Features of the calcium oscillations such as frequency and amplitude were quantified using ScreenWorks Software Peak Pro.

Results: Cortical 3D spheres from control and DISC1 mutant cells contain neurons and astrocytes with highly synchronized activity that begins after 2 weeks of differentiation. Both control and DISC1 spheres respond to excitatory and inhibitory compounds, which indicates a fully functional neuronal circuit. DISC1 spheres exhibit reduced frequency and increased amplitude of calcium oscillations compared to control. DISC1 spheres exhibit a ~60% decrease in calcium oscillation frequency compared to control ($P < .001$) and a ~2.4-fold increase in oscillation amplitude ($P < .001$). Calcium oscillations increased over the course of the analysis, but the difference between control and DISC1 mutant remained even at the 12-week timepoint. Reduced frequency of calcium oscillations is consistent with the finding that DISC1 neurons have decreased synapse number and impaired synaptic vesicle release. We found that Forskolin increases the frequency of calcium oscillations in both control and DISC1 spheres.

Conclusions: Here we highlight a human iPSC-derived platform for measuring spontaneous activity that is amenable to high-throughput screening. We found that iPSC-derived spheres containing a DISC1 frameshift mutation exhibit reduced frequency and increased amplitude of calcium oscillations compared to control. This finding is consistent with this DISC1 mutation causing decreased synapses and impaired synaptic vesicle release. We found that acute treatment with Forskolin increased frequency of DISC1 spheres to similar frequency as control, which demonstrates that DISC1 spheres have the capacity to fire like control. However, we also observed that Forskolin is non-specific for the DISC1 phenotype as the frequency of control spheres was also increased. Future studies will aim to identify compounds that will only increase the frequency of DISC1 spheres. This assay could be utilized for disease-modeling efforts to determine if iPSC-derived spheres from patients with sporadic forms of psychiatric disorders demonstrate similar or other alterations in spontaneous network activity. Finally, this platform and phenotype are amenable to high-throughput screening and may provide a new-approach for drug discovery.

Keywords: hIPSCs, Disease modeling, Phenotypic Screening

Disclosure: Janssen Research & Development, Employee

W82. Chronotype and Cellular Circadian Rhythms Predict the Clinical Response to Lithium Maintenance Treatment in Patients With Bipolar Disorder

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Background: Bipolar disorder (BD) is a serious mood disorder associated with circadian rhythm abnormalities. Risk for BD is genetically encoded and overlaps with the systems that maintain circadian rhythms. Lithium is an effective mood stabilizer treatment for BD, but only a minority of patients fully respond to monotherapy. Presently, we hypothesized that lithium-responsive BD patients (Li-R) would show characteristic differences in chronotype and cellular circadian rhythms compared to lithium non-responders (Li-NR).

Methods: Selecting patients from a prospective, multi-center, clinical trial of lithium monotherapy, we examined morning vs. evening preference (chronotype) as a dimension of circadian rhythm function in 183 Li-R and Li-NR BD patients. In a subset of 59 patients, we measured circadian rhythms in fibroblasts longitudinally over 5 days using a bioluminescent reporter (Per2-luc). We then estimated circadian rhythm parameters (amplitude, period, phase) and the pharmacological effects of lithium on rhythms in cells from Li-R and Li-NR donors.

Results: Compared to Li-NRs, Li-Rs showed a difference in chronotype, with higher levels of morningness. Evening chronotype was associated with increased mood symptoms at baseline, especially depression and insomnia. Cells from Li-R patients were more likely to exhibit a short circadian period, a linear relationship between period and phase, and period shortening effects of lithium. Common genetic variation in the IP3 signaling pathway may account for some of the individual differences in the effects of lithium on cellular rhythms.

Conclusions: We conclude that circadian rhythms may influence response to lithium in maintenance treatment of BD. The circadian clock might contain novel molecular targets for mood stabilizer drugs, and/or present the means for improved diagnostic testing to personalize mood stabilizer treatments.

Keywords: Lithium, Circadian Rhythm, Bipolar Disorder, Pharmacogenetics, Molecular Genetics

Disclosure: Nothing to disclose.

W83. Electric Stimulation Increases Expression of Leukemia Inhibitory Factor in Astrocytes via Adenosine Triphosphate Receptor P2X2

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Background: Electroconvulsive therapy (ECT) is often used and much effective for psychiatric disorders. However, the action mechanisms of ECT remain unclear. We previously reported that Transcription Factor 7 (TCF7) was increased in peripheral bloods of the patients successfully treated by ECT. TCF7 is a key factor of Wnt signaling pathway, which regulates adult hippocampal neurogenesis. Adult hippocampal neurogenesis is involved in the pathophysiology of psychiatric disorders and increased by electric stimulation (ES) in animal models of psychiatric disorders. In addition, most of neurogenic factors are secreted from astrocytes. Astrocytes play a pivotal role in adult hippocampal neurogenesis. Therefore, we hypothesized that ECT increases neurogenic factors, which can activate Wnt signaling pathway, in astrocytes. To test this hypothesis, we investigated the effects of ES and adenosine triphosphate (ATP), a main neuron/glia crosstalk-mediating factor and secreted from neurons in response to ES, on mRNA expressions of Leukemia Inhibitory Factors (LIF) and Fibroblast Growth Factor 2 (FGF2), which activate Wnt signaling pathway and increase adult hippocampal neurogenesis, in primary-cultured mouse astrocytes.

Methods: Primary-cultured mouse astrocytes were prepared from neonatal mouse forebrain and cultured with DMEM-based medium. The expressions of FGF2 and LIF were measured with quantitative RT-PCR. The concentration of ATP and the strength of ES were decided by using incorporation of calcium as a biomarker of the activation of astrocytes. Calcium incorporation into astrocytes was measured with Fluo 4-AM, a cell-permeant calcium indicator.

Results: ATP rapidly and remarkably increased mRNA expression of LIF, but not FGF2. On the other hand, ES had no direct significant effect on mRNA expressions of LIF and FGF2. Therefore, ES may increase mRNA expression of LIF in astrocytes via ATP. Next, we investigated the involvement of P2X2, an ATP receptor and recently shown to be involved in depression-like behaviors in mice, in the increasing effects of ATP on mRNA expression of LIF in astrocytes. P2X2 knockdown with siRNA surely canceled the increasing effects of ATP on mRNA expression of LIF.

Conclusions: P2X2 may mediates ES/ATP-mediated increase of LIF expression in astrocytes. These results suggest that P2X2-mediated increase of LIF expression in astrocytes may mediate a curative effect of ECT on mood disorders. Elucidating the detailed mechanisms underlying P2X2-mediated increase of LIF expression is expected to result in the identification of new therapeutic targets of psychiatric disorders.

Keywords: ECT, Wnt signaling, Astrocyte, Adenosine Triphosphate (ATP), Leukemia Inhibitory Factor (LIF)

Disclosure: Nothing to disclose.

W84. Initial Cellular Trigger for the Rapid Antidepressant Actions of Rapastinel

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Background: Rapastinel, previously referred to as GLYX-13, is a novel NMDA receptor (NMDAR) positive modulator that exerts rapid antidepressant actions in rodent models and phase 2 clinical trials. Importantly, rapastinel has a lower propensity to induce dissociative and psychotomimetic side effects than ketamine. Recent studies demonstrate that the actions of rapastinel require BDNF release, mTORC1 signaling, and synapse formation in the medial prefrontal cortex (mPFC). However, the initial cellular trigger for rapastinel and downstream signaling pathways remain unknown. In particular, whether rapastinel acts directly on principal neurons in the mPFC or indirectly on GABA neurons to disinhibit excitatory neurons is unknown.

Methods: To address this question, we conducted cell specific knockdown of GluN2B in principal glutamate vs. GABA inhibitory neurons in the mPFC using male CAMKII-Cre and GAD67-Cre mice and AAV2-viral mediated, Cre-dependent expression of GluN2B shRNA in the mPFC. After allowing time for AAV-GluN2B shRNA expression and knockdown to occur, the influence of rapastinel on behavior was tested in the forced swim test (FST), novelty suppressed feeding test (NSFT), and female urine sniffing test (FUST). The influence of rapastinel on NMDA receptor channel activity in glutamate neurons was directly tested in slices of mPFC using patch clamp electrophysiology. Male C57BL/6 J mice were used for all other experiments.

Results: The results demonstrate that knockdown of GluN2B on glutamatergic but not GABAergic neurons ($p < 0.05$, Two-way ANOVA post hoc Tukey's multiple comparison test) blocks the antidepressant effects of rapastinel in the FST, NSFT, and FUST. Conversely, the behavioral actions of ketamine in the FST were blocked by knockdown of GluN2B on GABAergic but not glutamatergic neurons ($p < 0.05$). Patch clamp studies conducted in layer V pyramidal neurons in mPFC slices are consistent with these findings; the results demonstrate that bath application of rapastinel causes a dose dependent enhancement of the response to a submaximal dose of NMDA while ketamine completely blocks the NMDA response as expected.

Conclusions: The results demonstrate that the antidepressant actions of rapastinel are mediated by GluN2B containing NMDAR on glutamatergic neurons indicating rapastinel acts directly to enhance the function and plasticity of principal neurons in the mPFC. In contrast, our recent studies demonstrate that ketamine acts via blockade of GluN2B/NMDAR on GABAergic neurons, consistent with an indirect, disinhibition hypothesis for the actions of ketamine. Patch clamp slice studies also demonstrate direct enhancement of NMDA induced currents in layer V mPFC neurons. These findings are also consistent with in vivo microdialysis studies demonstrating that ketamine, but not rapastinel causes a rapid, transient increase in extracellular glutamate. Ongoing experiments are evaluating the potential cell-type specific role of GluN2B vs. GluN2A, as well as other downstream signaling pathways in the antidepressant effects of rapastinel.

Keywords: Rapastinel, Rapid Antidepressant, NMDA Receptor, Medial Prefrontal Cortex

Disclosure: Nothing to disclose.

W85. The Efficacy of Adjunctive Treatment With Buprenorphine/Samidorphan Combination on MADRS Item Scores in Patients With Major Depressive Disorder from 2 Randomized Control Trials

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Background: Major depressive disorder (MDD) is a debilitating illness associated with motivational deficits, emotional distress, and impairment in social and occupational function.1 Buprenorphine/samidorphan combination (BUP/SAM) is an investigational opioid system modulator for adjunctive treatment for MDD that has shown efficacy versus placebo in reducing total Montgomery–Åsberg Depression Rating Scale (MADRS) in placebo-controlled

clinical studies.2-4 The MADRS is a validated 10-item scale developed to be sensitive to symptom change with tricyclic antidepressants5 The MADRS addresses 10 aspects related to symptoms of MDD: reported sadness, apparent sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Given the novel mechanism of BUP/SAM, there is scientific interest in evaluating the individual items of the MADRS that contribute to its efficacy. In this post-hoc analysis, we investigate the specific MADRS items contributing to the BUP/SAM efficacy observed in MDD patients in 2 placebo-controlled studies.

Methods: The FORWARD-4 (NCT02158533) and FORWARD-5 (NCT02218008) studies compared adjunctive BUP/SAM 2 mg/2 mg with placebo in patients with MDD who had an inadequate response to antidepressant therapy (ADT) during their current major depressive episode. Patients continued with ADT throughout the studies. Both studies employed a sequential parallel comparison design (SPCD) to minimize bias in the ascertainment of placebo non-response. The studies that consisted of two double-blind placebo-controlled randomized stages: stage 1 assessed all patients randomized at study entry and stage 2 assessed those patients who did not respond to placebo during stage 1 and were randomized in stage 2. Only FORWARD-5 achieved its primary endpoint. Data from the BUP/SAM 2 mg/2 mg and placebo arms from both studies were pooled to allow more power for this post-hoc analysis.

The average BUP/SAM versus placebo difference in change from baseline to week 3 through end-of-treatment score (MADRSAVG) and BUP/SAM versus placebo difference change from baseline to end-of-treatment score (MADRSEOT) were computed for each item of the MADRS for each randomized stage. Estimates of the drug-placebo differences in each stage were averaged using equal weights to derive the overall primary comparison, reported as the least-squares mean differences (LSMD) between BUP/SAM and placebo.

Results: This post-hoc analysis included data from 651 stage 1 patients (122 in the BUP/SAM group and 529 in the placebo group), and 231 stage 1 placebo non-responders who were re-randomized to stage 2 (117 in the BUP/SAM group and 114 in the placebo group) from the FORWARD-4 and FORWARD-5 studies. Baseline demographics were similar across treatment groups, stages, and studies. Mean total MADRS scores were 31.9 in the BUP/SAM group and 31.8 in the placebo group at baseline of stage 1, and 26.1 in the BUP/SAM group and 26.9 in the placebo group at baseline of stage 2.

The LSMD from placebo in the MADRSAVG total score was −1.8 ($P = 0.004$). The MADRS items that demonstrated MADRSAVG change versus placebo were pessimistic thoughts (−0.4, $P < 0.001$), reported sadness (−0.2, $P = 0.012$), apparent sadness (−0.2, $P = 0.029$), inner tension (−0.2, $P = 0.013$), lassitude (−0.2, $P = 0.015$), inability to feel (−0.2, $P = 0.013$), and suicidal thoughts (−0.2, $P < 0.001$). MADRSAVG changes in reduced sleep, reduced appetite, and concentration difficulties were −0.1 or smaller and not statistically significant compared with placebo. No individual MADRS item showed worsening on BUP/SAM versus placebo.

The LSMD from placebo in the MADRSEOT total score was −1.8 ($P = 0.010$). The MADRS items demonstrating MADRSEOT change versus placebo were similar to those for MADRSAVG.

Conclusions: Within the limitations of this post-hoc analysis, adjunctive treatment with BUP/SAM 2 mg/2 mg, an investigational opioid system modulator resulted in improvements in scores in all the psychological symptoms of depression, and suicide ideation, as would be expected from an antidepressant.

Keywords: Buprenorphine, MADRS, Major Depressive Disorder, Samidorphan

Disclosure: Alkermes, Inc., Employee

W86. A Retinal Brain Circuit for Mood Regulation

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Background: We have shown previously that light can regulate mood in animals directly through the intrinsically photosensitive retinal ganglion cells, also known as ipRGCs. ipRGCs are atypical photoreceptors that operate on their own similar to the classical photoreceptors, rods and cones involved in image formation. Despite the previous progress, we had no idea which brain regions are involved in mediating the effects of light on mood.

Methods: We used several methods, which included modified genetic mouse lines, viral tracing, chemo and optogenetics, as well as several behavioral paradigms to define the brain regions required for the modulation of mood in response to light.

Results: Our results identified a subset of ipRGCs, that are defined by the lack of Brn3b expression and project to the SCN, are sufficient to drive light-mediated cognitive deficits, without disrupting the SCN clockwork machinery. An SCN-independent pathway mediates light-induced mood changes, through ipRGC input to the perihabenular nucleus (PHb) of the dorsal thalamus. PHb neurons project to well-characterized mood-regulating centers. Furthermore, the PHb is both necessary and sufficient for driving the effects of light on affective behavior.

Conclusions: These findings reveal two distinct retinal-brain pathways that mediate the direct effects of light on mood and cognition.

Keywords: Depression, Light Therapy, Retina, Circadian, Sleep

Disclosure: Nothing to disclose.

W87. Brain Extracellular Matrix Genes are Dysregulated in Major Depressive Disorder

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Background: As one of the leading causes of disease burden and disability in the world, Major Depressive Disorder (MDD) is a major public health concern. Mounting evidence suggests that structural brain abnormalities may contribute to MDD pathology, although this remains a largely unexplored area of research. The extracellular matrix (ECM) plays a crucial role both in providing structural support to the brain and facilitating synaptic plasticity. We hypothesized that alterations to this complex network of proteins surrounding neurons and glial cells could regulate morphological processes that may be involved in MDD.

Methods: To understand the role of the brain ECM in MDD, we analyzed transcriptional profiles from the nucleus accumbens (NAc) and prefrontal cortex (PFC) in postmortem brain tissue of humans with MDD and matched controls. In order to develop a translational approach to study any identified ECM-specific gene targets from MDD patients, we also assessed transcriptional profiles of mice exposed to chronic variable stress (CVS).

Results: Numerous ECM-specific genes were identified as being differentially expressed in our datasets. For the greatest translational value, only genes identified as being similarly differentially regulated across species were selected for further investigation. Of such genes, relatively few were regulated similarly in the two brain regions studied and in both sexes. For example, Cyr61 and Htra1

were identified as being dysregulated only in males and specifically in the PFC or NAc, respectively. Interestingly, Cyr61 and Htra1 are both highly enriched in astrocytes.

Conclusions: We are currently developing the viral and transgenic tools necessary to manipulate these genes selectively within astrocytes of the PFC or NAc in order to study their functional role in stress responses at the behavioral and molecular levels. Our findings thus far support the hypothesis that the ECM of the brain is a potentially important mediator of stress responding that is influenced in both a sex- and region-specific manner.

Keywords: Major Depressive Disorder (MDD), Extracellular Matrix, Chronic Stress, Medial Prefrontal Cortex, Nucleus Accumbens

Disclosure: Nothing to disclose.

W88. Validation and Mapping of the Suicidal Ideation and Behavior Assessment Tool (SIBAT)

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Background: Suicide is a mounting public health concern and the incidence of suicide has increased over the past two decades in the United States, with nearly 45,000 deaths attributed to suicide in 2016. This highlights the critical need to identify persons at potential risk for suicide so that effective interventions can be made. Additionally, measures are needed to track changes in suicidality in clinical trials, to measure safety (to confirm that new agents being evaluated do not increase suicide ideation and/or risk) and to measure efficacy (to determine if an agent reduces suicidality and/or clinician-assessed suicide risk). Better methods are required to systematically track changes in suicidal ideation and behavior (SIB), especially over short time intervals (e.g., within hours), and to establish efficacy of newer agents with potentially rapid-onset efficacy, as existing scales have not been validated for this purpose. The SIB Assessment Tool (SIBAT) is designed to measure rapid SIB changes in clinical trial settings and is intended to capture both patient-reported and clinician-rated information relevant to suicidal ideation, behavior, and risk. This report from a validation study summarizes the SIBAT reliability properties and its mapping to the Columbia Classification Algorithm of Suicide Assessment (C-CASA).

Methods: The SIBAT is a computerized clinical outcome assessment instrument comprising 8 modules that capture information on patient demographics, known suicide risk factors, history of suicidal behavior and current suicidal ideation, and clinician assessment of the severity of suicidality and suicide risk. These modules are organized separately reflecting these categories and susceptibility to short-term change: 5 modules are designed for completion by the patient, and 3 by the clinician. This psychometric validation study (NCT03085108) was a cross-sectional study conducted to evaluate the psychometric properties of the SIBAT and validate its use in participants at various severities of suicidality. Participants with different SIB severities ($n = 130$, among them $n = 71$ were clinically depressed) completed the 5 SIBAT patient-reported modules during a single study visit. The clinician-raters reviewed these modules, performed a semi-structured interview (guided by prompts within the SIBAT), and completed the clinician-reported modules. These included single item questions addressing Clinical Global Impression of Severity of Suicidality Revised (CGI-SS-R), CGI of Imminent Suicide Risk (CGI-SR-I), CGI of Long-Term Suicide Risk (CGI-SR-LT), Frequency of Suicidal Thinking (FoST), and Clinical Judgment of Optimal Suicide Management (CJOSM). Intra- and inter-rater reliability was evaluated using recorded interviews from the rater-reliability sample ($n = 25$). After ≥ 2-weeks from initial assessments, the patient self-reported modules and interview videotapes were re-rated by original clinician-raters for intra-rater reliability evaluation and assessed using weighted kappa statistics. Ten novel clinician-raters performed ratings for inter-rater reliability, which was estimated using comparison of original and novel-ratings and analyzed using intra-class correlation coefficient (ICC). The intra- and inter- rater reliability analyses were also performed on the subset of participants who were regarded as clinically depressed ($n = 16$). Responses to the SIBAT patient-rated modules and data from clinician interviews were mapped using a computerized algorithm to the various versions of the C-CASA. Comparison of SIBAT C-CASA mapping to that of the Columbia-Suicide Severity Rating Scale (C-SSRS) was evaluated using weighted kappas and percent agreement.

Results: The levels of suicidality of the participants (mean age, 38 years) ranged from not suicidal to extremely suicidal. Clinician-raters had a mean (SD) experience of 8.7 (6.65) years in assessing suicidal patients. For intra-rater reliability of the SIBAT clinician ratings (i.e. CGI-SS-R, CGI-SR-I, CGI-SR-LT, FoST, and CJOSM), weighted kappas ranged from 0.64 to 0.76, indicating good levels of agreement within the two ratings by the original clinical-raters. Based on the inter-rater reliability analyses for the SIBAT Clinical Global Impressions (i.e. CGI-SS-R, CGI-SR-I, CGI-SR-LT, FoST, and CJOSM), ICCs ranged from 0.68 to 0.82, indicating adequate to excellent agreement across raters. Comparable results on intra- and inter-rater reliability were observed for the clinically depressed sample. In comparing the C-CASA mapping from the SIBAT and the C-SSRS, weighted kappas ranged from 0.56-0.72 and percent agreement ranged from 46.15 to 73.08.

Conclusions: The intra-rater and inter-rater reliability analyses demonstrate that the SIBAT Clinical Global Impressions have good levels of agreement within and across clinician- raters. The information collected within the SIBAT can be used to successfully map to the C-CASA. These findings support the application of the SIBAT as a validated instrument in clinical trials and other studies for the assessment of suicidality especially over short time intervals.

Keywords: Suicidal Ideation and Behavior Assessment Tool, Rater Reliability, Validation

Disclosure: Johnson & Johnson, Employee

W89. Effect of Esketamine Nasal Spray on Cognitive Functioning in Participants With Treatment-Resistant Depression: Results From Five Phase 3 Studies

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Background: Esketamine is a glutamate receptor antagonist being developed as a nasal spray for therapy in treatment-resistant depression (TRD). The effect of esketamine nasal spray (ESK) on cognitive functioning in participants with TRD was assessed in five phase 3, multicenter studies: 4 randomized, double-blind (DB) studies (DB1, DB2, DB3 and DB4) and 1 open-label (OL) study (OL1).

Methods: Adult participants (18-64 years [≥ 65 years for DB4]) with moderate-to-severe depression and non-response to ≥ 2

antidepressants in the current depressive episode were enrolled. In the DB studies, participants were randomized either to ESK (28 [DB4 only], 56, or 84 mg) or placebo; and initiated a new, OL oral AD. The OL study (OL1), evaluated ESK (28 [≥ 65 years], 56 or 84 mg) and newly-initiated oral AD. At the end of the 4-week induction phase (IND), responders in DB1 and DB2 were eligible to enter DB3; elderly participants in DB4 were eligible to enter OL1. DB3 included a 4-week OL IND (ESK 56 or 84 mg) + newly-initiated oral AD, a 12-week optimization phase (OP) to individualize treatment session frequency (once-weekly or once every other week), and a maintenance phase (MA) in which participants receiving ESK + oral AD were randomized to either continue ESK + oral AD or be switched to oral AD + placebo until relapse or study completion. OL1 included a 4-week OL IND (28, 56, or 84 mg) + newly-initiated oral AD followed by up to a 48-week OP/MA. The follow-up phase (FU) was 2-4 weeks (DB1, DB2), 2-weeks (DB3, DB4), and 4-weeks (OL1).

Cognitive assessments including the Cogstate computerized test battery (Detection [DET], Identification [IDN], to assess simple reaction time [processing speed] and choice reaction time, respectively; One-Card Learning [OCL] to assess visual memory; One Back Memory [ONB], to assess working memory; and Groton Maze Learning[GML] to assess executive function) and Hopkins Verbal Learning Test-Revised (HVLT-R) were administered at baseline, day 28, early withdrawal (EW), and FU (week 2) in DB1, DB2, DB4, and at 12 week intervals, beginning from week 16 (DB3) and 20 (OL1), EW and FU (2 weeks and 4 weeks for DB3 and OL1, respectively). Cognitive assessments were also administered at EW visits, and at baseline and day 28 for direct entry participants in DB3 or OL1. All tests were conducted predose. Descriptive statistics were used to summarize scores and change from baseline at each timepoint.

Results: Mean performance in the ESK and placebo groups on each cognitive test either improved from baseline or remained at levels similar to baseline at both the end of DB treatment (day 28) and during the FU, in each acute study (DB1 [n = 102 to 112 per group], DB2 [n = 94 to 108 per group], DB4 [n = 42 to 65 per group]). The one exception was in elderly participants (DB4); a slight slowing of reaction time (RT) versus baseline on the DET (simple RT) at day 28 was observed in both the ESK + oral AD group (n = 56; mean [SD] slowing [log10 ms] = 0.0182 [0.14018]; effect size, change from baseline, Cohen's d = 0.12) and in the oral AD + placebo group (n = 58; mean [SD] slowing [log10 ms] = 0.0245 [0.13437] Cohen's d = 0.18).

In each long-term study (DB3, OL1), cognitive performance was similar to baseline or slightly improved during OP/MA or MA treatment, including those treated with either ESK + oral AD or placebo + oral AD in the DB MA phase of DB3 (n = 133 to 145 per group at LOCF endpoint). The one exception was in elderly participants in OL1; performance on simple and choice RT tests (DET and IDN) indicated slight slowing of mean RT vs. baseline, beginning at week 20 (n = 72) and continuing through week 52 endpoint (n = 24). Performance of elderly participants on all tests of higher cognitive function (OCL, ONB, GML, HVLT-R) either remained stable or improved throughout OL1.

Elderly participants had high intraindividual variability in RT on both DET and IDN. For elderly participants who completed through 52 weeks (n = 24), Cohen's d for endpoint (week 52) change from baseline for DET = 0.52; for IDN = 0.47. Among completers without slowed RT (z-score < -1.5) at baseline (n = 20), 7 participants demonstrated consistent slowing on DET or IDN as the study progressed (slowing on ≥ 2 consecutive post-baseline DET or IDN scores [Reliable Change Index (RCI) < −1.645] without a subsequent RCI ≥ -1.645); 2 of the 7 had slowing of RT at endpoint on both DET and IDN. No participant had impaired RT on DET or IDN (z-score < −1.5) at both endpoint and FU assessments.

Conclusions: Overall, cognitive functioning remained stable in adult and elderly participants with TRD during both acute and long-term treatment with either ESK + oral AD or oral AD + placebo. Specifically, performance of both younger adult and elderly participants remained stable or improved on all tests of higher cognitive function. Based on group mean scores, elderly participants in OL1 exhibited slowing of RT during OP/MA treatment but none exhibited impaired RT at both endpoint and FU. Further analyses of intraindividual variability of RT among elderly participants in OL1 are ongoing.

Keywords: Antidepressant, Cognitive Functioning, Intranasal Esketamine, Treatment-resistant depression

Disclosure: Johnson & Johnson, Stock / Equity

W90. Pramipexole in Bipolar Disorder: Targeting Cognition (PRAM-BD; R01MH102257)

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Background: Converging evidence suggests that patients with bipolar disorder (BD) suffer from deficits in neurocognitive functioning that persist, despite remission of acute affective symptoms. These impairments contribute directly to functional disability, highlighting the need for interventions above and beyond standard treatments in order to achieve a full inter-episode recovery. Few studies have been conducted that target cognition as a primary outcome in BD.

We previously completed a controlled cognitive enhancement trial of a dopamine (D2/D3) agonist (pramipexole) in 42 patients with BD. The primary analyses resulted in an overall negative trial but highlighted a subgroup of patients for whom pramipexole was beneficial, improving working memory over 8 weeks (Burdick et al. J Clin Psych, 2012). Based on these promising results, we designed a second study and enriched the sample for cognitive impairment at baseline to focus on those patients for whom treatment is most warranted.

Methods: This is a 2-site, federally-funded, randomized, placebo-controlled, adjunctive, 12-week trial in a relatively large cohort of affectively-stable men and women with BD. Our primary outcome measure was the composite score from the MATRICS Consensus Cognitive Battery, and we included a battery of additional measures, with a focus on reward processing. Weekly mood and side effect ratings were conducted, and cognition was assessed at baseline, week 6 and again at week 12. Mixed models will be used for final analyses.

Results: A total of 103 subjects were consented, of which 67 subjects were randomized, 54 subjects completed through at least week 6, and 51 subjects completed the full 12-week trial. The sample has a mean age = 45.4 + /- 11.5, is 59% female, and is 52% Caucasian.

The study has closed to enrollment; however, the unblinded data are being prepared for final analyses currently. Here, we are able to present preliminary results by treatment group (A versus B). All results presented in December will be updated based upon unblinded data analyses to begin in late August 2018.

We are pleased to report that there have been no serious adverse events and no unanticipated problems. Nausea was the most commonly reported adverse event (6% of participants in each group; no group differences). There were no exacerbations of manic symptoms or "switches" reported.

Baseline cognitive data suggest that the cohort of patients enrolled in this trial have deficits across multiple cognitive domains that range from 1/2 (Social Cognition) to 1.0 standard deviation below normal (all other domains) at study entry,

consistent with the enriched sample design. Treatment groups are well-matched at baseline for all demographic and clinical features (all p-values > .19); however, significant group differences in baseline cognition in the domains of Reasoning and Problem Solving (t = 2.02; p = .048) and Social Cognition (t = 2.15; p = .036) were noted and will be handled appropriately in analyses. Initial repeated measures analyses indicate moderate effect size changes for MCCB Composite (Cohen d = .40 for Group A) versus very small changes (Cohen's d = .10 for Group B) over 12 weeks. Likewise, Group A shows moderate improvement on Processing Speed (d = .45) relative to Group B (d = .23). Results from more comprehensive mixed models will be presented once the unblinded data are available.

Conclusions: We anticipate this completer sample to be sufficiently powered to detect the same range of effect sizes that we have previously reported for pramipexole (Burdick et al. J Clin Psych, 2012). The current sample was explicitly enriched via the design of the study at the outset and we expect this to further increase the likelihood of detecting a positive effect on cognition. We will also be able to address the effects of the study drug on reward processing and neural targets associated with pramipexole's action on the D3 receptor, as we have previously shown in BD patients (Burdick et al. Neuropsychopharmacology, 2013). Data will provide new insights into how modulation of the D3 receptor might influence cognitive symptoms in patients with the long-term goal of improving quality of life.

Keywords: Cognition, Bipolar Disorder, Pramipexole, Dopaminergic System

Disclosure: Nothing to disclose.

W91. P2X7 Receptor Antagonism Modulates the Processing of Faces Based on Emotion Expression in Major Depressive Disorder

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Background: Major depressive disorder (MDD) is associated with negative processing biases characterized by preferential processing of negative information. These biases are demonstrated through behavioral and neuroimaging paradigms where differences in responses are dependent on emotional valence of stimuli, and there is evidence that these effects reverse following antidepressant treatment. JNJ-54175446 is a selective, brain penetrant P2X7 receptor antagonist being assessed for use in the treatment of mood disorders. Here we assess the effects of JNJ--54175446 on negative processing biases in MDD patients as measured using an emotional face memory paradigm and electroencephalography (EEG).

Methods: Patients with MDD who met DSM-IV or V diagnostic criteria participated in a 10-day trial using JNJ-54175446. Participants were randomized into treatment group A [10 M/16 F; Mean age = 36(+SD12); Mean HAMD = 19 (+4); Day 1-600 mg JNJ-54175446; Day 2-10- 150 mg/day], treatment group B [9 M/17 F; Mean age = 39(+14); Mean HAMD = 16(+5); Day 1-3- placebo; day 4- JNJ-54175446 600 mg; day 5-10- 150 mg] or placebo [7 M/10 F; Mean age = 42(+12); Mean HAMD = 21(+4); Day 1-10- placebo]. A separate P2X7 PET study suggests 80% target engagement at this dose. EEG was collected during an emotional face memory task using the B-Alert X24 wireless system (ABM) at baseline prior to dosing and was repeated on day 10. During acquisition happy (H), sad (S) and neutral (N) faces (n = 36) were presented in a pseudo-random sequence and were shown a second time. During the test phase, the 36 acquisition stimuli were presented interspersed with 36 emotional distractor faces, and subjects indicated whether they had seen each face previously. Raw EEG data were bandpass filtered (0.1 to 50 Hz), epoched (time-locked to each stimulus), separated by stimulus type, and averaged together to compute event related potentials (ERP). Each epoch was defined from 1 second pre- to 2 seconds post- stimulus onset. Baseline was removed from each epoch and trials with abnormal amplitude were filtered out using EEGLAB software. Amplitudes were measured for the ERP components of interest, separated by emotion (N, S, and H) and testing session (days 1 and 10). Emotional processing biases (S vs H; S vs N; H vs N) were assessed at baseline in the ERP components linked to stimulus processing (N170/N280) across all subjects/groups combined. Compound effects were assessed within the 3 groups separately on change in amplitudes of S, H and N faces, and on change in processing biases by comparing baseline measures with day 10 measures. Within group change in bias measures then were compared across groups. Statistical analyses were conducted using within- and between- subject ANOVA and t-tests, and significance was defined at $p < 0,05$, uncorrected.

Results: On average, across groups, baseline response amplitudes were larger to S than to H faces ($p < 0.05$) in the N170 response component (parietal, occipital sites). Similarly, response amplitudes were larger to S than to N faces (S > N; $p < 0.05$) in the N170 and N280 ERP components (frontal, central, parietal). These results demonstrate a negative emotion processing bias towards S faces at baseline. H faces also produced larger responses than N faces (frontal). Within groups, only the S > N contrast remained significant in all individual groups at baseline (trend level for the N170 in the placebo group), thus S > N is the emotional bias estimate considered for compound effects (described below).

Following JNJ-54175446 administration, widespread decreases in the response amplitude during perceptual processing (N280) of S, H and N faces between baseline and day 10 ($p < 0.05$) were seen in groups A (central, frontal, parietal) and B (central, frontal, parietal). In the placebo group, the N280 response to S faces (temporal) and to N faces (central) increased ($p < 0.05$) and did not change in response to H faces ($p > 0.05$). The S > N effects in N170 and N280 seen at baseline were absent on day 10 in treatment groups A and B ($p > 0.05$). The reduction in S > N bias was greater for both the N170 and N280 at day 10 in the treatment group A than in placebo ($p < 0.05$), suggesting a significant decrease in the negative processing bias following JNJ-54175446. While the S > N bias was absent on day 10 in group B, the comparison to placebo did not reach statistical significance ($p > 0.05$). Both treatment groups showed longer reaction times (RT) to S than N faces at baseline, consistent with an emotional processing bias, and this effect was absent at day 10. However, no difference in RT was seen in the placebo group.

Conclusions: These findings demonstrate that baseline emotional processing biases towards sad faces in perceptual components of the ERP (N170; N280) are reduced by P2X7 receptor antagonism. Baseline processing biases were evident with larger responses to sad faces than to neutral and happy faces, supporting the presence of a negative processing bias. The absence of a S > N bias by day 10 in the JNJ-54175446 treatment groups suggest that these negative biases are reduced by P2X7 receptor antagonism. The within-group treatment effects only reached significance compared to placebo within group A, which may suggest that group B did not receive sufficient dosing by end of study to maximally affect the emotional bias. Overall these findings suggest that baseline negative emotional processing biases in patients with MDD are sensitive to P2X7 receptor antagonism. Similar effects on emotion processing biases have been observed in relation to antidepressant treatments.

Keywords: Mood Disorders, P2X7, Clinical Trial

Disclosure: Janssen Pharmaceuticals, Employee

W92. Early Clinical Characterization of a Novel, Brain-Penetrant, Selective P2X7 Receptor Antagonist, JNJ-54175446, in Healthy Subjects and Participants With Major Depressive Disorder: A New Mood Stabilizer?

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Background: The P2X7 receptor is a novel target to treat mood disorders. P2X7 receptor activation leads to the release of the pro-inflammatory cytokine IL-1β and thereby may play a role in the inflammatory diathesis of mood disorders. In animal models, blocking P2X7 receptor activity attenuated the effects of psychostimulants and (sub-chronic) stressors on locomotor and sucrose preference behaviors respectively, and showed a significant and long-lasting delay in kindling development in a chemically induced kindling model. These observations suggest that P2X7 receptor antagonists share some pharmacodynamic effects in common with mood stabilizing agents.

Methods: JNJ-54175446, a selective and brain-penetrant P2X7 receptor antagonist, was evaluated in 312 men and women including 69 patients with depression. Its pharmacokinetic/pharmacodynamic (PK/PD) relationship was characterized in healthy subjects by measuring the inhibition of IL-1β release from LPS/BzATP-stimulated peripheral blood samples and positron emission tomography (PET) using a P2X7 receptor-selective PET ligand, 18F-JNJ-64413739. Its potential for mood stabilization was evaluated following a 20 mg D-amphetamine challenge in healthy subjects and total sleep deprivation in MDD subjects. Subjective effects were evaluated using visual analogue scales (VAS), self-report scales (e.g. Snaith-Hamilton pleasure scale [SHAPS]), and biomarker (including electroencephalography [EEG]) assessments.

Results: EC50 values for inhibition of IL-1β and displacement of 18F-JNJ-64413739 were comparable, 67 ng/mL and 44 ng/mL, respectively. PK/PD analyses suggested complete P2X7 receptor blockade throughout the dosing interval at dose levels ranging from 50 – 150 mg once daily (qd). Results from the challenge studies are presented as mean values ± SD for placebo versus JNJ-54175446; [N] = subject number. Administration of 150 mg JNJ-54175446 qd attenuated acute mood effects of D-amphetamine in healthy subjects (VAS mood 14.8 ± 3.38 [16] versus 17.4 ± 1.01 [11]; $p < 0.05$) as well as mood elevation following total sleep deprivation (SHAPS 4.9 ± 3.22 [16] versus 7.4 ± 4.05 [24]; $p < 0.05$). JNJ-54175446 did not significantly affect amphetamine-induced motor behaviors or stimulated EEG alpha power and trended to increase reward sensitivity. JNJ-54175446 was safe and well-tolerated in all studies and mild headache and nausea were identified as possibly treatment related.

Conclusions: JNJ-54175446, administered at clinically meaningful dose levels, antagonized psychostimulant- and sleep deprivation-induced mood elevations. Behavioral activation by psychostimulant administration translated into an effect on subjective experiences in humans, differentiating P2X7 antagonists from dopamine D2 antagonists. We hypothesize that P2X7 antagonists may afford a new drug class characterized by mood stabilizing effects, along with a good safety and tolerability profile.

Keywords: P2X7, Mood Disorders, Microglia, F-18 PET Imaging

Disclosure: Janssen R&D, Employee

W93. Suicide Ideation Trajectories in the Months Before and After a Suicide Attempt: Investigation From Step BD

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Background: Suicide is a major public health threat and one of the leading causes of death in the United States. Suicidal behavior is a common psychiatric emergency with many patients presenting for treatment after a suicide attempt; additionally, Bipolar Disorder (BD) is known to be associated with considerable suicide risk. Suicide behavior is often understood as a type of diathesis-stress model, in which a vulnerable individual is exposed to specific provocation that culminates in a suicidal crisis. Understanding the dynamic processes of symptom changes before and after a suicide attempt may provide further insight into the suicidal crisis itself, laying the groundwork for future phenomenology or intervention studies. Large clinical trials, such as the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial, provide opportunities to describe symptom trajectories before and after a suicide attempt.

Methods: All data were drawn from the STEP-BD study which followed 4,360 patients with BD across 22 academic psychiatry centers over seven years, a subset of whom attempted suicide during the trial. The primary focus of this analysis was changes in suicidal ideation (SI), measured by the Clinical Monitoring Form (CMF), before or after a suicide attempt. To do this, we used general linear mixed models with a two-piece linear function of time (in months) corresponding to pre- and post-event (suicide attempt) trends.

Results: A total of 1,231 SI ratings from 216 individuals were analyzed ($n = 395$ pre-attempt, 126 circa-attempt, and 710 post-attempt). A positive but non-significant trajectory was observed prior to the attempt, followed by a decreasing trajectory after the attempt, meaning that SI was fairly stable before the attempt, but decreased after the attempt [$t(717) = 4.24$, $p = < .0001$]. Other potential suicide risk factors, including depressed mood, agitation and anxiety followed a similar pattern, meaning that they decreased post-attempt. When compared to a randomly selected sample of non-attempters ($n = 648$), the results suggested that the level of SI among attempters was reduced to that of non-attempters by approximately 2 months post-attempt [$t(2154) = 1.88$, $p = .06$].

Conclusions: The majority of the suicide literature focuses on factors which predict a suicide attempt. Here, we modeled change in symptoms both before and after a suicide attempt, which is particularly relevant for psychiatric clinicians who often treat patients just after suicidal behavior. Results highlight that SI, depressed mood, agitation and anxiety decrease after a suicide attempt. In this sample, the SI symptoms were indistinguishable from non-attempters by 2 months post-attempt. This decrease in symptoms could be the result of treatments initiated after an attempt but can also represent the resolution of the short-lived suicidal crisis. Implications of these results for both researchers and clinicians will be discussed, particularly whether it would be possible to initiate treatment for the SI, depressed mood, anxiety or agitation before the patient commences a suicidal behavior, thereby avoiding a suicide attempt.

Keywords: Suicide Assessment, Suicide, Bipolar Disorder

Disclosure: Nothing to disclose.

W94. A Multi-Level Approach to Interoception and Psychopathology

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Background: The development of the Research Domain Criteria (RDoC) has emphasized a multi-level approach to understanding psychiatric illness across the dimensions of biology, behavior, and self-report. Interoception is not explicitly included in such dimensional frameworks for phenotyping mental illness, even with evidence of providing direct associations biological and psychological processes in numerous disorders including depression and anxiety (Paulus & Stein, 2010). The current study explored multi-level relationships between interoception and psychopathology across the spectrums of depression and anxiety using a data driven approach.

Methods: Participants were selected from the first 500 subjects of the Tulsa 1000, a naturalistic study focused on assessment and prediction of psychiatric outcomes across different levels of analyses in 1000 treatment-seeking individuals with mood and/or anxiety, substance use, and eating disorders, and their healthy comparators (Victor et al., 2018). Age, BMI, and sex matched cohorts of individuals with depression (DP; $n = 58$), comorbid depression and anxiety (CO; $n = 58$) and their healthy comparators (HC; $n = 58$) were selected for a total sample size of 174 participants (sex: 52.9% female, mean age: 33.1 ± 10.8 years, mean BMI: 27.9 ± 5.3).

Each participant completed numerous tasks designed to probe interoception across different levels of analyses. Self-report level: scales assessing symptom severity (PHQ-9 for depression, OASIS and ASI-physical concerns for anxiety, and MAIA for interoceptive awareness). Behavioral level: three interoceptive tasks (heartbeat tapping task, inspiratory breath hold, and cold pressor) with physiological, behavioral, and self-report variables collected. Neurobiological level: an interoceptive attention task during fMRI scanning at 3 Tesla. During the interoceptive attention condition participants focused on the intensity of sensations from their heart or stomach, and during the exteroceptive control condition attended to the intensity of a color change on the viewing screen. Interoceptive brain activity was indexed via the contrast between the interoceptive and exteroceptive conditions. Previous work has demonstrated that this task reveals attenuated insula activation in depression (Avery et al, 2014, Simmons et al, 2017), and therefore this region was the focus of analysis in the current study.

Data driven approach: Group factor analysis (GFA) is a Bayesian tool used to describe relationships between groups of variables in a data set. We utilized the GFA package in R (version 3.3.2) to examine the relationships between 53 variables in each of the following blocks of variables: self-report (11 variables), interoceptive attention (6), breath hold (15), cold pressor (10), and heartbeat tapping (11). To examine the stability of the factor solution we conducted a series of GFAs that rely on sampling to arrive at the optimal factor solution. Factors were considered robust if they appeared in 90% of the individual GFAs. GFAs were performed first on the combined set of 174 individuals, followed by a cluster analysis using k-means (3 clusters) to determine if cohort status could be identified. Performance was evaluated with the Rand Index, a measure corresponding to how well the clusters divided the cohorts (an index of 1 indicates perfect clustering). Finally, these robust factors were examined for relationships with psychopathology utilizing Elastic Net regression, in order to evaluate whether clinically relevant variables not included in the GFA, such as age, BMI, self-reported PROMIS measures, default mode and salience network functional connectivity, were related to the robust GFA factors.

Results: The GFA explained 25.4 ± 2.2% of the variance in the 174-participant data set through 7 robust factors. Only one of these factors showed a cross-block relationship between the interoceptive attention fMRI task and the heartbeat tapping behavioral task, explaining 1.2 ± 0.07% variance. K-means clustering revealed poor group identification, with a Rand index of 0.07. Examining clustering more closely revealed that 51% of the HCs grouped in one cluster and 62% of the COs in different cluster. The DP cohort showed a wider split across the clusters, with 46% of DPs being clustered with the CO cohort, and the remaining DP group evenly split in the remaining two clusters. However, the exploratory Elastic Net regression analyses revealed strong relationships between all seven factors and the PROMIS anxiety ($R^2 = 0.62$) and PROMIS depression ($R^2 = 0.59$) scores. The remaining self-report measures showed small to moderate R^2 values ranging from 0.1 (PROMIS Physical Function) to 0.5 (PROMIS positive affect and well-being). The additional measures in the physiological and neurological domains showed weak relationships, such as age and BMI ($R^2 < 0.02$), salience ($R^2 = 0.05$) and default mode ($R^2 = 0.08$) network functional connectivity.

Conclusions: Based on a multi-level Bayesian group factor analytic approach there is some evidence for latent variables that are related to both psychopathology and interoceptive characteristics. These latent variables showed strong relationships with depression and anxiety symptoms. Although the variances accounted for by these latent variables is relatively small, these results support the idea that interoceptive functioning contributes to the psychopathology of mood and anxiety disorders.

Keywords: Depression, Anxiety, Interoception, RDoC, Research Domain Criteria

Disclosure: Nothing to disclose.

W95. Informing the Complex Association Between Depression Symptom Severity and Neurocognitive Function in Geriatric Major Depressive Disorder

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Background: Major depressive disorder is a chronic neuropsychiatric disease, with a heterogenous constellation of symptoms, that results in significant morbidity and mortality. The symptoms in MDD range across multiple domains including mood, physiologic, and neurocognitive. Over the past three decades, there has been inconsistent findings regarding how MDD affects neurocognitive function. Some research has suggested that depression symptom severity results in greater neurocognitive inefficiency and impairment, whereas other research has found no such relationship. Indeed, we previously found in an adult cohort with treatment resistant MDD that there was no association between depression symptom severity and objective cognitive performance. Importantly, there is limited information regarding the presence or absence of such associations in geriatric depression. Thus, the purpose of this study was to determine the association between depression symptom severity and neurocognitive function in elderly adults with MDD.

Methods: The Prolonging Remission in Depressed Elderly (PRIDE) study was a multicenter, randomized study of an

individualized continuation ECT schedule combined with pharmacotherapy to enhance long-term outcomes in elderly adults with MDD. The study had two phases. In Phase 1, patients received acute ECT 3x weekly combined with venlafaxine. In Phase 2, those who remitted in Phase 1 were randomized to receive pharmacotherapy (venlafaxine and lithium) alone or the combined modalities (pharmacotherapy and continuation ECT). Elderly adults (age > 60) with MDD, based on semi-structured diagnostic interviews including the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) or the Mini-International Neuropsychiatric Interview (MINI), were enrolled in the study. All participants provided written informed consent for this IRB approved investigation before completing study procedures. The 24-item Hamilton Rating Scale for Depression (HRSD24) was used to document depression symptom severity. Specific neurocognitive instruments included the Autobiographical Memory Interview-Short Form (AMI-SF), California Verbal Learning and Memory Test-II (CVLT-II), Delis-Kaplan Executive Function System Verbal Fluency Test, Dementia Rating Scale-2nd Edition Initiation Perseveration Index, Mini Mental State Examination (MMSE), Stroop Color and Word Test, and the Trail Making Test. With the exception of the AMI-SF, all neuropsychological variable raw scores were converted into demographic- adjusted scores. The HRSD24 and the neurocognitive measures were completed at baseline, before the patient underwent any treatment procedures. Descriptive statistics were used to characterize the demographic, neurocognitive and clinical features of the study sample who met selection criteria and began Phase 1. Means and standard deviations are presented for continuous variables, and frequency distributions are presented for discrete variables. Pearson correlation coefficients and corresponding 95% confidence intervals (CI) around the correlation coefficient were computed to describe the association between baseline neurocognitive variables and initial depression severity (HRSD24 total score). All statistical tests were two-tailed with alpha = 0.05, and correlations were defined as small (r < .30), medium (r = .31 - .6), or large (r > .61 based on standard guidelines.

Results: At baseline, depression severity as rated on the HRSD24 was negatively associated with global cognitive function (r = -0.14, 95%CI: -0.01 - -0.26, p = 0.04), cognitive processing speed (r = -0.15, 95%CI: -0.02 - -0.27, p = 0.03), autobiographical memory recall (r = -0.29, 95%CI: -0.17 - -0.40, p < 0.0001), verbal learning (r = -0.16, 95%CI: -0.03 - -0.28, p = 0.02), delayed free recall of learned words (r = -0.18, 95%CI: -0.05 - -0.30, p = 0.01), and initiation/perseveration (r = -0.18, 95%CI: -0.05 - -0.30, p = 0.01). Though statistically significant, the correlations were relatively weak.

Conclusions: To our knowledge, this is one of the first studies to examine the relationship between depression symptom severity and neurocognitive function in elderly adults with MDD. The study found small and clinically unmeaningful associations between baseline depression severity and neurocognitive function. These findings are consistent with our prior research in adults and extend them into an elderly adult population. Such findings suggest that while MDD can affect neurocognitive function, it is weakly related to depression severity. As such, other aspects of MDD including the number of depressive episodes, specific symptom clusters (e.g., melancholia), depressive episode chronicity may be more strongly related to neurocognitive outcomes. Although the finding was negative, it helps to guide direction of future investigations. Indeed, future research is warranted to understand the dynamic relationship between aspects of MDD and neurocognitive functions. Such research would benefit from large-scale computational and machine learning data analytic methods that can determine the linkage between MDD symptomatology, neurocognitive functions, and underlying neuromechanisms.

Keywords: Neuropsychology, Major Depression, Geriatric Depression

Disclosure: TMS Health Solutions, Honoraria, Self, NIMH, Grant

W96. Safety of Real World Use of Ketamine for Depression

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Background: Parenterally administered ketamine has demonstrated robust efficacy in treating depression, but short duration of the antidepressant effect requires repeated administration for continued benefit. The safety of repeated parenteral ketamine for depression is not currently known. The objective of this study was to investigate the safety of repeated parenteral ketamine for depression using a survey of experienced providers of ketamine.

Methods: An electronic survey was sent to providers of parenteral ketamine identified from two online directories of ketamine providers. The survey was designed to assess their experiences and specifically, their encounter with adverse effects such as behavior indicating addiction to ketamine, bladder dysfunction cognitive deficits, mania, adverse psychological effects, hypertension, and psychotic symptoms.

Results: The survey was sent to 69 providers, 36 responded (52% response rate) and 27 were included in the analysis. The providers included in the analysis reported treating 6630 patients with parenteral ketamine for depression. Over 2100 received 11 or more individual parenteral treatments. The providers reported a low incidence of adverse effects: addictive behaviors (0.1%), bladder cystitis (0.1%), cognitive decline (0.03%), and psychotic symptoms (0.03%). Only 0.7% of patients experienced an adverse effect that required discontinuation of ketamine treatments, the most frequent of which was psychological distress during the dissociative experience. Features inherent in the responses of providers strongly suggest that under-reporting of adverse effects did not occur.

Conclusions: This is the first study that describes the real-world experiences of providers who have used ketamine to treat depression. The overall rate of side effects appears low and suggests that long-term treatment of depression with ketamine may be reasonably safe. A limitation of this study is that the data are derived from providers' responses to a survey rather than direct clinical data. Long-term prospective studies investigating the safety of chronic ketamine treatment for depression are needed.

Keywords: Ketamine, Depression, Antidepressant

Disclosure: Nothing to disclose.

W97. Fluoxetine Exposure in Adolescent and Adult Female Mice Decreases Cocaine and Sucrose Preference Later in Life

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Background: Preclinical literature indicates that exposure to antidepressant medications, during early stages of development, results in long-term altered behavioral responses to drugs of abuse (Iñiguez et al., 2015, Sci Rep, 5:15009). However, to date, these studies have been conducted in male subjects primarily. This is surprising, given that females, when compared to males, are more likely to be diagnosed with mood-related disorders, and thus, be prescribed with antidepressants. Therefore, the objective

of this study is to assess whether exposure to the selective serotonin reuptake inhibitor fluoxetine (FLX) results in long-lasting alterations in sensitivity to the rewarding properties of cocaine and sucrose, using female mice as a model system.

Methods: Adolescent (postnatal day [PD]-35) and adult (PD70) female C57BL/6 mice were exposed to FLX (in their drinking water, 250 mg/l) for 15 consecutive days. Twenty-one days later (PD70 + and PD105 +, respectively), mice were assessed on behavioral responsivity to cocaine (0, 2.5, 5, 7.5 mg/kg) using the conditioned place preference paradigm, or their sensitivity to a 1% sucrose solution using the 2-bottle choice test.

Results: Data was analyzed with ANOVA techniques, with antidepressant pre-exposure and cocaine post-exposure as sources of variance, followed with Tukey post hoc tests. Our results indicate that female mice pre-exposed to FLX during adolescence or adulthood displayed reliable conditioning to the cocaine-paired compartment, in a dose-dependent manner. However, when compared to respective age-matched controls, antidepressant pre-exposure decreased the magnitude of conditioning at the 5 ($p < 0.05$, $R2 = 0.21$) and 7.5 mg/kg ($p < 0.05$, $R2 = 0.51$) cocaine doses. Similarly, independent of age of antidepressant pretreatment, FLX-pretreated mice also displayed a decrease in sucrose preference ($p < 0.05$, $R2 = 0.62$), without altering total liquid intake ($p > 0.05$).

Conclusions: Collectively, our results suggest that exposure to FLX, in adolescent and adult female C57BL/6 mice, leads to prolonged decreases in sensitivity to the rewarding properties of both drug- and natural-rewards. This data further highlights the need for investigations assessing the potential enduring neurobiological side effects that may arise later in life, as a result of antidepressant exposure, in a sex dependent manner.

Keywords: Fluoxetine, Cocaine, Anhedonia, Female

Disclosure: Nothing to disclose.

W98. A Survey on Treatment Resistant Depression From Patients' Perspective

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Background: We aim to improve our understanding of treatment resistant depression (TRD) from the patient's perspective in a large population of depressive subjects.

Methods: We designed and deployed an antidepressant efficacy survey to 23andMe research participants to evaluate the overall treatment outcome and the contribution of pharmacotherapy if receiving both non-pharmacotherapy and pharmacotherapy within the same episode. Duration taking a list of commonly used antidepressant, depression characteristic, comorbidity, stressful life events, early childhood traumatic experience, trigger, family history, social support, and symptoms during the two weeks in the episode when depressive symptoms were most severe and persistent were assessed. A survey participant is classified as having TRD if he/she took at least two medications for 5-6 weeks and did not respond to pharmacotherapy. In contrast, treatment responsive subjects (or non-TRD (NTRD)) are defined as responding to pharmacotherapy and taking two or fewer medications for more than 3-4 weeks.

Results: Approximately 43,000 consented research participants completed the survey. The TRD patients tend to have younger age of onset, spend more time being depressed in their life times, have longer average episode duration, and have residual symptoms between episodes. TRD patients tend to endorse anxious and melancholic features more so than mixture features. TRD patients tend to have higher co-morbidity of various psychiatric conditions and have endorsed experiencing more stressful life events than NTRD patients.

Conclusions: We identified depression characteristic, comorbidity, stressful life events, and early childhood traumatic experience that distinguish TRD patients from NTRD. Overall, TRD patients suffer far greater disease burden than NTRD.

Keywords: Depression, Treatment Resistant Depression, Comorbidity

Disclosure: Janssen R&D, LLC, Employee

W99. Emotions and Brain Function are Altered up to One Month After a Single High Dose of Psilocybin

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Background: Psilocybin acutely impairs negative emotion identification (e.g. fearful faces) and facilitates positive emotion identification (Kometer et al., 2012). Psilocybin also acutely decreases brain activity in regions implicated in emotions and depression (e.g. anterior cingulate, amygdala, and hippocampal complex; Kraehenmann et al., 2015, 2016; Preller et al., 2016; Kaelen et al., 2016). If acute changes in emotional function and associated neural circuitry persist after clearance of psilocybin from the body, this may account for reports of increased positive mood up to 14 months after psilocybin administration in healthy individuals (Griffiths et al., 2008, 2011), and reduction in depression and anxiety symptoms 3 to 6 months after psilocybin administration in cancer patients (Griffiths et al., 2016; Ross et al., 2016) and patients with treatment resistant depression (Carhart-Harris et al., 2016). Though acute effects of psilocybin have been investigated, little is known about the persisting effects of psilocybin on emotional information processing and neural circuitry, which is the focus of this open-label pilot study.

Methods: 9 volunteers (Age: 22-44, $M = 30$, $SD = 7.2$; 6 F/3 M) with minimal prior experience with psychedelics such as psilocybin were administered a high dose of psilocybin (25 mg/70 kg). These volunteers completed the amygdala reactivity task (Hariri et al., 2002, 2003) and the emotion recognition task (Gur et al., 2002) while blood-oxygenation level-dependent (BOLD) signal was measured using functional magnetic resonance imaging (fMRI) one day before (baseline), one week after, and one month after psilocybin. Volunteers also completed the Dispositional Positive Emotion Scale (DPES; Shiota et al., 2006), Depression, Anxiety, and Stress Scale (DASS; Lovibond & Lovibond, 1995), trait form of the State Trait Anxiety Inventory (STAI; Spielberger et al. 1983), Profile of Mood States (POMS; Shacham et al., 1983), and Positive and Negative Affect Schedule, form X (PANAS-X; Watson & Clark, 1994) at these same timepoints. Participants completed the Tellegen Absorption Scale (TAS; Tellegen & Atkinson, 1974), Emotion Regulation Questionnaire (ERQ; Gross & John, 2003), Big Five Inventory (BFI; John et al., 2008), and Brief Affective Neuroscience Personality Scale (BANPS; Barrett et al., 2013) at screening and one month after psilocybin. A paired t-test was used to determine the persisting effects of psilocybin on personality measures (TAS, ERQ, BFI, and BANPS). A one-way ANOVA with timepoint as a factor (baseline, 1-week post, and 1-month post psilocybin) was used to determine the persisting effects of psilocybin on BOLD measures and self-report measures.

Results: Psilocybin increased positive emotional traits (trait absorption from TAS: 29% increase, $d = 1.89$; conscientiousness from BFI: 8% increase, $d = 1.21$; care from BANPS: 8% increase, d

= 0.97) and reduced negative emotional traits (neuroticism from BFI: 14% reduction, d = 0.61; anger from ANPS: 5% reduction, d = 0.45; fear from ANPS: 11% reduction, d = 0.58; and suppression from ERQ: 17% reduction, d = 0.72). No negative emotional traits were increased.

Psilocybin also decreased negative emotional functioning one-week post-psilocybin (stress from DASS: 58% reduction, eta^2 = 0.71; trait anxiety from STAI, tension, depression, anger, and total mood disturbance from POMS also reduced) while the negative affect factor of the PANAS-X was reduced at both 1-week and 1-month post-psilocybin. Psilocybin increased self-report measures of positive emotional functioning (DPES measures Joy, Content, Pride, Compassion, and Amusement increased, all eta^2 > 0.6) at both 1 week and 1-month post-psilocybin compared to baseline. Thus, psilocybin increased positive emotional functioning and decreased negative emotional functioning, effects that persist for 1 month.

Psilocybin also altered the neural correlates of emotional functioning over time. Psilocybin decreased BOLD activity measured during the amygdala reactivity task (faces > shapes; Hariri et al., 2002, 2003) in left anterior insula and right parahippocampal gyrus at 1-week post-psilocybin, medial prefrontal cortex at 1-month post-psilocybin, and midcingulate cortex at both 1 week and 1-month post-psilocybin ($p < 0.005$, $k = 10$). BOLD activity measured while identifying negative emotional faces during the emotion recognition task [negative > neutral faces] decreased in the ventral lateral prefrontal cortex, right middle frontal gyrus, bilateral amygdala, and primary visual cortex, while it increased in precuneus, retrosplenial cortex, medial prefrontal cortex, and dorsal lateral prefrontal cortex 1 week after psilocybin ($p < 0.005$, $k = 10$). BOLD activity also increased in the dorsal anterior cingulate while identifying negative emotional faces one month after psilocybin ($p < 0.005$, $k = 10$).

Conclusions: Psilocybin substantially increased self-report and trait measures of positive emotion and substantially decreased measures of negative emotion for at least one month in healthy individuals. Psilocybin also decreased activity in response to negative emotional stimuli in limbic brain regions typically associated with monitoring salient and negative stimuli, while increasing activity in response to negative emotional stimuli in brain regions involved in cognitive control of emotions. These effects may underlie observed, long-term therapeutic effects of psilocybin administration.

Keywords: Psychedelic Medicine, Psilocybin, Affective Neuroscience, Functional MRI (fMRI)

Disclosure: Nothing to disclose.

W100. Myo-Inositol Levels and KCNH7 Gene in Mood Disorder

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Background: Genetic vulnerabilities play a role in the etiology of mood disorders although the mechanisms from genes to clinical symptoms remain unclear. In a discovery study of four Amish families (n = 27 family members) with a high frequency of mood disorders, a functional variant of the potassium channel H7 gene (rs78247304 of KCNH7) was found to be significantly associated with the mood disorder phenotype. In animal studies, depression phenotypes from genetic manipulation of voltage-gated potassium channel subunit genes is associated with reduced myo-inositol levels, a metabolite known to be related to mood disorders. The current study aimed to test whether the KCNH7 association with mood disorders can be replicated in a larger Amish cohort, and to use magnetic resonance spectroscopy (MRS) to assess whether myo-inositol, a metabolite previously linked to depression, may be associated with this potassium channel genetic variant.

Methods: MRS in medial prefrontal cortex / anterior cingulate cortex was performed in 142 Old Order Amish participants, 41 of which had a diagnosis of mood disorders. Mood disorders include major depressive and bipolar diagnoses. Levels of myo-inositol and six other brain metabolites were measured, and rs78247304 was genotyped.

Results: Myo-inositol levels in participants with mood disorder were significantly lower compared to non-psychiatric controls ($F = 9.2$, $p = 0.003$). The KCNH7 genotype was associated with mood disorders ($X2 = 4.9$, $p = 0.026$). Myo-inositol levels were different between the three KCNH7 genotypes with the minor allele homozygotes having a lower level (5.9 ± 0.8) than the heterozygotes (7.9 ± 0.3) who had a lower level than the major allele homozygotes (8.3 ± 0.1) ($F = 3.4$, $p = 0.036$).

Conclusions: These findings further support the link between KCNH7 and mood disorders and suggest that myo-inositol may be considered as a potential in vivo biomarker indexing the biological path from KCNH7 to mood disorders.

Keywords: Myoinositol, Mood Disorder, Potassium Channel

Disclosure: Nothing to disclose.

W101. Genome Wide DNA Methylation in the Neuronal Fraction of the Prefrontal Cortex from Depressed, Suicide, and Normal Control Subjects

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Background: Suicide is a major public health problem, as 40,000 people die of suicide alone in the United States each year. Although there are several studies of psychosocial factors associated with suicide, neurobiological mechanisms associated with suicide are not well understood. Some recent studies suggest abnormalities of HPA function in suicide while other studies suggest epigenetic modifications such as increased DNA methylation of certain HPA axis genes. To further evaluate these abnormalities, we analyzed HPA axis genes such as the glucocorticoid receptor (NR3C1), mineralocorticoid receptor (NR3C2), and corticotropin releasing factor (CRF) in post-mortem brains of suicide victims. Numerous studies suggest that NR3C1 is epigenetically regulated in the post-mortem prefrontal cortex (PFC) of suicide victims. To further examine epigenetic mechanisms, we performed DNA methylation analysis of neuronal DNA in the prefrontal cortex obtained from depressed suicide victims and normal control subjects.

Methods: Analysis of DNA methylation was performed on post mortem brain samples (PFC-Brodmann area 9) from 24 depressed suicide subjects and 24 normal control subjects. These subjects were diagnosed according to DSM IV criteria based on psychological autopsy. mRNA and protein expression of the DNA methylating (DNMTs) and demethylating (TETs) enzymes were determined using qRT-PCR and Western Blotting techniques, respectively. Genome wide methylation (5mC) levels in the PFC were performed using Infinium MethylationEPIC BeadChip which allows for the quantitative determination of 5mC at specific sites of promoters, enhancers, and other gene regions. The goal was to determine changes in 5mC levels in neurons in the PFC in suicide relative to normal control subjects. The NeuN-tagged neuronal

nuclei were isolated using fluorescence activated cell sorting using a BD MoFlo Astrios cell sorter and the application of appropriate filters to maximize the yield of NeuN-positive nuclei. DNA was isolated using a commercially available DNA isolation kit (Universal kit from Zymo Research) and fragmented using an ultrasonicator. The fragmented DNA was oxidized with bisulphite modification for subsequent annealing to the illumina EPIC chip.

Results: We analyzed the levels of DNMTs and TET enzymes in RNA from 24 depressed suicide and 24 normal control post-mortem PFC samples. We observed that while DNMT1 was increased, the levels of TET2 mRNA were decreased in the depressed suicide group. FACs analysis of human nuclei stained with an anti-NeuN antibody and DAP 1 showed 99% pure neuronal nuclei. There were a total of 865,859 CpG sites on the EPIC Array. After removal of CpGs that were either undetected, contained CpGs on the X or Y csomes, contained SNPs, or mapped to more than one site (potentially cross-reactive), a total of 787,689 sites remained which were analyzed for differential DNA methylation. Surrogate variable analysis was performed to look for correlations between samples that are not attributed to the suicide vs. control grouping (e.g. post-mortem interval and brain pH did not affect DNA methylation). Following FDR correction, there were no widespread methylation changes particularly, changes from fully methylated to fully unmethylated CpGs. In addition to assessing individual CpGs for methylation differences, we also tested for differentially methylated regions (regions that were concordantly methylated). DMRcate identified 1,516 regions of at least 2 significant CPGs in close proximity and 1,317 of these regions had minimum FDR p-values < 0.05.

We used gene ontology analysis of genes associated with methylated CPGs to examine if any functional classes of genes were differentially methylated. We used the gometh for these functions from the missMethyl package. Some of biological process gene ontology terms associated with our data include: signaling, system immune response, positive regulation of nervous system development, chromatin organization, etc. We found many genes differentially regulated in our system. In the Ingenuity pathway analysis, we found a total of 333 genes that were differentially regulated in the neuron development category. Several Hub genes, such as BCl2, β-catenin (CTNNB1), and GSK3β were identified. We also found a MAP kinase, MAPK1 and NRP1 as HUB genes, along with PRKCA or the PKCα. Using KEGG Pathway analysis, we identified several Hub genes that include SGK1 and GSK3β, as well CTNNB1. In the Immune system process category, there were 620 genes differentially regulated. Some of the Hub genes again were CTNNB1, IGF2R, CREBBP, HDAC1, and MEF2C.

Conclusions: Our studies suggest that abnormalities in genome wide DNA methylation profiles in neurons of the PFC may be associated with suicidal behavior. Bioinformatic analysis of the differentially methylated genes observed in DS and NC post-mortem samples (BA9) highlight pathways containing enrichment of genes related to HPA axis, neuron development, and immune system processes. We are currently in the process of validating some of the highly significant and differentially regulated genes such as FKBP4, CRFBP, CTNNB1, CD-44, etc.

This work was supported by a grant from the NIMH to Dr. GN Pandey (grant number RO1MH091079-01A1).

Keywords: DNA Methylation, Prefrontal Cortex, Epigenetic Modification

Disclosure: Nothing to disclose.

W102. Can Neuron-Related Blood Proteins, Indicating the Levels of Neuron-Derived Exosomes (NDE), Become an Objective Evaluation Tool for Depression?

Abstract not included.

W103. Differential Effects of Ketamine on Brain Activity During Emotional Processing in MDD Patients With Versus Without a History of Suicide Attempt

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Background: Suicidal thinking is common in major depressive disorder (MDD), and about 60 percent of suicide attempts are associated with a mood disorder. Ketamine, a glutamatergic modulator, has recently been shown to decrease suicidal ideation. However, little is known about whether brain function in MDD patients with a history of suicide attempt differs from non-attempters and how ketamine administration affects brain function. In this study, we investigated differences in the impact of ketamine on functional MRI (fMRI) blood-oxygen-level dependent (BOLD) signal during emotional processing between depressed patients with and without a history of suicide attempt. Previous research on brain function during emotion-related tasks has shown both increased and decreased brain activation in different regions in suicide attempters, including altered activity in cingulate and frontal areas. In a prior study comparing these MDD participants to healthy controls, an interaction between group and drug was found, with depressed patients showing reduced activation to emotional stimuli post-ketamine compared to post-placebo in prefrontal cortex, insula, and cingulate, with the opposite finding in healthy participants. We predicted that ketamine would affect brain activation differentially in patients with a history of suicide attempt in emotion processing regions of the brain.

Methods: This study included 30 unmedicated (both male and female) participants with MDD: 12 with a prior suicide attempt history (S-Hx +) and 18 without (S-Hx-). As part of a randomized double-blind placebo-controlled protocol, participants received an infusion of ketamine (0.5 mg/kg) and placebo, two weeks apart. Two days after each infusion, participants completed an emotional processing task in a 3 T MRI scanner. In this task, faces with emotional expressions were presented one at a time for 750 ms. In one block, participants judged the emotion of the face as positive or negative, and in the other block, judged the gender of the face. To analyze the BOLD fMRI data, a linear mixed-effects model was used with group, drug, and task-specific conditions as factors. We used a voxel-level threshold of $p < 0.001$ and an FWE-corrected cluster-level threshold of $p < 0.01$.

Results: We found a group by drug interaction in several areas throughout the brain ($pFWE < 0.01$). In the right frontal cortex, right insula, bilateral thalamus, and bilateral precuneus, ketamine increased activation in S-Hx + but decreased activation in S-Hx-. In other regions including left frontal and occipital areas, the opposite pattern was found. Additionally, there was a group by drug by task condition interaction in frontal and cingulate regions ($pFWE < 0.01$), in which activation that differed between group and drug also varied by the task condition of judging emotion versus gender of the faces. In S-Hx + in the judging emotion condition, ketamine decreased activity, while it increased activity in the gender condition. The opposite pattern was found in S-Hx-.

Conclusions: Our findings demonstrated that ketamine has differential effects on brain activity in S-Hx + and S-Hx- patients. Specifically, S-Hx + patients had less activation than S-Hx- post-placebo in anterior insula and prefrontal cortex, which then reversed post-ketamine. Compared to our prior findings in healthy

participants, these results may indicate a greater normalization of brain function in S-Hx- patients, although these participants were not directly compared in this analysis. Overall, our results were found in several frontal cortical regions and areas involved in emotional processing. In particular, the findings in the anterior insula may indicate involvement of the salience network in suicidal behavior. These findings may contribute to a better understanding of brain activity associated with treatment for suicidal individuals.

Keywords: Ketamine, Functional MRI (fMRI), Suicidality, Emotional Processing, Major Depressive Disorder (MDD)

Disclosure: Nothing to disclose.

W104. Ketamine's Rapid Antidepressant Action is Associated With Changes in the Functional Connectivity of the Habenula

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Background: Ketamine's strong and rapid antidepressant properties have shown great promise to treat severe forms of major depressive disorder (MDD). A recently proposed mechanism of action of ketamine involves the inhibition of N-methyl-D-aspartate receptor-dependent bursting activity in the habenula (Hb). The Hb is a diencephalic structure that acts as neuroanatomical hub regulating brain areas central for motivation and goal-directed behavior. In this study, we investigated changes in the functional connectivity of the Hb in patients with MDD following treatment with ketamine.

Methods: Resting-state functional connectivity (FC) magnetic resonance imaging was acquired in 28 treatment-resistant unmedicated patients with MDD at baseline and one day after treatment with intravenous ketamine (0.5 mg/kg over 40 min). A seed-to-voxel functional connectivity analysis was performed with the Hb as a seed-of-interest. Comparisons in Hb FC values at baseline and 24 h after treatment were made. Relationships between changes in FC of the Hb and depressive symptom severity measured using the Montgomery- Åsberg Depression Rating Scale (MADRS) were examined.

Results: There was a significant increase in FC between the left Hb and left hippocampus (pFDR < 0.001), and between the right Hb and clusters in the right temporal (pFDR = 0.02), and right paracingulate cortices (pFDR = 0.03) one day following ketamine infusion compared to baseline. In contrast, there was a reduction in FC between the left Hb and bilateral clusters in the parietal and dorsolateral prefrontal cortex (DLPFC). A reduction in MADRS scores post-ketamine were associated with a reduction in FC between the Hb and clusters in the DLPFC, insula and superior frontal gyrus bilaterally.

Conclusions: Ketamine is associated with changes in the FC of the habenula that may help explain the improvement in depressive symptoms. These preliminary results are consistent with models of antidepressant action that involve the modulation of habenula projections to cortico-limbic areas.

Keywords: Ketamine, fMRI Functional Connectivity, Major Depressive Disorder, Habenula

Disclosure: Nothing to disclose.

W105. Electroconvulsive Therapy Modulates Grey Matter Increase in a Hub of an Affect Processing Network

Abstract not included.

W106. Cognitive Flexibility Under Frustration: Transdiagnostic Neural Mechanisms of Irritability

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Background: Irritability, defined as an increased proneness to anger and frustration relative to one's peers (Brotman et al., 2017; Leibenluft, 2017), has been linked to later depression and anxiety and long-term impairment such as high suicidality and low education and income attainment (e.g., Vidal-Ribas et al., 2016). Despite the impairing nature of irritability, little is known regarding its pathophysiology. One cognitive function germane to irritability is cognitive flexibility, the ability to inhibit a prepotent response and execute an alternative response to changes in the environment (Kenner et al., 2010; Kim et al., 2012); it is essential for higher-order cognitive functions such as decision-making, problem-solving, and emotion regulation (Davidson et al., 2006). Given that many irritable youth struggle with transitions and adapting flexibly and appropriately to changing environmental contingencies, particularly when frustrated (Leibenluft & Stoddard, 2013), paradigms that probe cognitive flexibility under a frustrating context may elucidate the neural mechanisms of irritability. Indeed, a previous study demonstrated that youth with irritability were less accurate compared to healthy volunteers (HV) on a task requiring cognitive flexibility (Dickstein et al., 2007). In addition, a few previous studies utilizing frustration paradigms in youth with irritability reported neural dysfunction in the frontal-striatal regions (Grabell et al., 2018; Perlman et al., 2015; Rich et al., 2011; Tseng et al., accepted) as well as amygdala and parietal cortex (Deveney et al., 2013). However, none of these examined cognitive flexibility. Here, we extended this research by studying the neural correlates of cognitive flexibility under frustration and their associations with irritability in a transdiagnostic sample.

Methods: This study included 68 youth with varying levels of irritability across four diagnostic groups: 26 disruptive mood dysregulation disorder (DMDD), 13 attention-deficit/hyperactivity disorder, 11 anxiety disorder, and 18 HV (mean age = 14.45 years; age range = 10 – 22 years; 61.8% males). Participants completed a modified Change-Signal task (Kim et al., 2012) while their functional magnetic resonance imaging (fMRI) data were acquired on a 3 T scanner. The task required participants to inhibit a prepotent response ("go"; 60% of the trials) and to substitute an alternative response ("change"; 40% of the trials) for the prepotent one. Frustration was evoked by manipulating the task difficulty such that the "frustrating" blocks had an error rate of 50% and the "non-frustrating" blocks had an error rate of 10% on the change trials. In addition, participants were given rigged feedback in the "frustrating" blocks (on 20% of correct "go" trials). Participants self-reported frustration at several points during the task using a 9-point Liker scale (1 = "not at all frustrated" to 9 = "extremely frustrated"). The average of parent- and child-report of the Affective Reactivity Index scale (Stringaris et al., 2012) was used as a dimensional measure of irritability.

We used the SPSS to analyze the behavioral data and the Analysis of Functional NeuroImages (AFNI) software (Cox, 1996) to analyze the fMRI data. For the behavioral data, we conducted repeated-measures analyses of covariance (ANCOVAs) to examine the associations of irritability with task performance (i.e., accuracy, reaction time [RT], change-signal reaction time [CSRT]) as well as self-rated frustration during task. For the fMRI data, we conducted whole-brain ANCOVAs to examine the association between

irritability and blood-oxygen-level-dependent (BOLD) signal changes on several task contrasts (e.g., go vs. change trials in the frustrating blocks; change trials in the frustrating vs. non-frustrating blocks). Given the wide age range of the sample, we also examined the moderating effect of age on the association between irritability and brain activation. We report clusters surpassing a prefrontal cortex (PFC) corrected threshold ($\alpha = .05$) at voxelwise $p = .001$ and $k > 26$ voxels via Monte Carlo cluster-size simulation (Cox et al., 2017).

Results: Behaviorally, levels of irritability were not associated with task performance in terms of accuracy, RT, and CSRT (ps > .05). However, irritability was related to more self-rated frustration during the frustrating vs. non-frustrating blocks ($r = .27$, $p = .03$).

Imaging analyses revealed that age moderated the association between irritability and neural activation in the left inferior frontal gyrus (IFG; xyz = -31, 6, -14, $k = 35$) during go vs. change trials in the frustrating blocks. Specifically, higher irritability was related to decreased IFG activation in older youth (i.e., age 15-22 years) but not younger youth (i.e., age 10-15 years).

Conclusions: Our data provide preliminary evidence to suggest that IFG dysfunction during cognitive flexibility when frustrated may mediate irritability in a transdiagnostic manner and that such IFG dysfunction varies with age. Our next step is to examine functional connectivity during this task and investigate whether functional connectivity patterns and specific networks (e.g., default mode, frontal-parietal, cingulo-opercular) in the frustrating blocks are more predictive of irritability symptom than those in the non-frustrating blocks.

Keywords: Irritability, Functional MRI (fMRI), Cognitive Flexibility, Frustration, Youth

Disclosure: Nothing to disclose.

W107. Examination of a Multimodal Marker of Major Depressive Disorder From Structural and Diffusion MRI

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Background: The goal of this study was to identify biomarkers of major depressive disorder (MDD), by relating neuroimage-derived measures to binary (MDD/control), ordinal (severe MDD/mild MDD/control), or continuous (depression severity) outcomes. As pointed out by Peterson & Weissman (2011), a biomarker for MDD could aid in diagnosis, the search for genetic and environmental causes, predicting course, identifying those at increased risk and developing the next generation of treatments. To address MDD heterogeneity, factors (severity of psychic depression, motivation, anxiety, psychosis and sleep disturbance) were also used as outcomes.

Methods: This study used multi-site, multimodal imaging (diffusion MRI, dMRI, and structural MRI, sMRI) with a cohort of 52 controls and 147 MDD patients. Critically, we use an additional cohort of 25 controls and 83 MDD patients for validation. Across training and validation sets, 118 males and 189 females were included. MRI images were acquired using 3 T scanners across 5 sites. Data for 217 participants were acquired from the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study (U01 MH092250, http://embarc.utsouthwestern.edu/). To ensure that the MDD sample was representative and as large as possible, data for an additional 90 participants were drawn from ten studies conducted at the New York State Psychiatric Institute/Columbia University Medical Center.

Region-wise cortical thickness was computed from the anatomical MRI for 68 Desikan-Killiany atlas regions (Desikan et al., 2006). Diffusion images were acquired using a single-shot EPI (echo planar imaging) sequence with either 64 or 25 collinear directions with 1 or 5 non-weighted images 25 collinear directions. Fractional anisotropy (FA), common measure used in dMRI to determine integrity of white matter fibers by estimating the direction of movement of water molecules, was extracted from dMRI images.

All image analyses were performed by a single image analysis lab within a standardized processing pipeline. All technicians were blinded to subject diagnoses.

Since the biological underpinnings of MDD are unknown, a large number of potential features were examined. For each subject, 225 features were included: age at evaluation, sex, handedness, 145 sMRI-based and 77 dMRI-based features.

Discrete measure: We evaluated two potential classification schemes: (1) Binary: MDD vs controls and (2) Ordinal: severe MDD vs mild MDD vs control. (68 patients had severe depression with a Hamilton Depression Rating Scale [HAMD] 17 item total score > 19.)

Continuous measure: This included depression severity (HAMD total score) and factors. Each factor is a sum of the products of the factor's HAMD items and corresponding loading values obtained from a previous factor analysis (Milak et al., 2005).

Different predictive model building techniques (penalized logistic regression [PLR], random forest [RF] and support vector machine [SVM]) were applied.

Results: The optimally performing classifier (SVM) had a misclassification rate of 26.0% (binary), accuracy of $52.2 \pm 1.69\%$ (ordinal) and correlation coefficient of $r = 0.36$ (p-value < 0.001, continuous). Across all classifiers, R2 values for prediction of any MDD factors were < 10%. Because of the low performance of both ordinal classification and predictive modeling, external validation analysis was only performed on the binary classifier and similar results were achieved in this external dataset. Four measures contributed to model accuracy across all models and analyses--two dMRI-based measures (average fractional anisotropy in the right cuneus and left insula) and two sMRI-based measures (asymmetry in the volume of the pars triangularis and the cerebellum).

Conclusions: From this study, we conclude: 1) Despite our use of multiple models with differing advantages, a large training dataset, and a separate validation analysis, the final overall model performance was too low for clinical application. 2) Although four features (mean fractional anisotropy in the right cuneus and left insula, asymmetry in the volume of the pars triangularis and cerebellum) were implicated across all analyses, low classification and prediction accuracy using these features indicates that they cannot represent the entire pathophysiology of MDD. However, they may be relevant for future investigations of MDD neurobiology. 3) It has already been suggested that dMRI-based measures cannot be used to distinguish MDD in large samples (K. S. Choi et al., 2014) and this could be one reason for the equivocal results to date. In agreement with lack of previous consensus among sMRI and dMRI findings in MDD, the results of our powerful, comprehensive approach suggest that the sMRI and dMRI features used here may not provide a usable marker for diagnostic classification or prediction of depression severity on their own.

To improve predictive power, future work would involve utilizing these study characteristics (large cohort, multimodality features, robust methods, external validation) to combine the four sMRI and dMRI measures implicated across all analyses with other potential neurobiomarkers such as those derived from PET and/or

EEG, or other behavioral measures. Such an approach could bring us closer to the first clinically relevant biomarker of MDD.

Keywords: Major Depressive Disorder (MDD), Magnetic Resonance Imaging, Diffusion Tensor Imaging (DTI), Structural MRI, Support Vector Machine (SVM)

Disclosure: Nothing to disclose.

W108. Emotion Regulation Circuitry in Bipolar Disorder and its Changes With a Targeted Psychobehavioral Intervention

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Background: Bipolar Disorder (BD) is associated with severe dysregulation of both negative and positive emotional responses, which contributes to worsening symptoms, poor prognosis and adverse outcomes, such as suicide. Abnormalities in a corticolimbic system that subserves emotion regulation (ER) have been demonstrated in the disorder. However, few neuroimaging paradigms used in the study of BD directly engage ER processes, particularly in response to stimuli of both negative and positive emotional valences. Using a novel task in which participants downregulated responses to emotional stimuli of both valences, we examined (1) corticolimbic functioning during ER across mood states of BD, and (2) changes in functioning of this brain system following treatment with a novel psychobehavioral intervention, Brain Emotion SelfMonitoring and Regulation Therapy (BE-SMART), that was designed to target ER difficulties of BD and their associated brain circuitry.

Methods: 57 individuals with BD (14-59 years, 23 euthymic, 22 depressed, and 12 in elevated mood states) and 63 healthy comparison (HC) subjects (14-58 years) completed functional magnetic resonance imaging (fMRI) scans while performing the ER task in which they were instructed to either "view" or to down-regulate ("decrease") their responses to faces depicting negative (fearful) or positive (happy) emotions. In a follow-up study, adolescents and young adults with BD (16-24 years) were scanned while performing the ER task before and after they were administered 12 weeks of BE-SMART focused on learning and practicing healthy behaviors including reappraisal to promote ER. Statistical Parametric Mapping (SPM12) software was used to preprocess and analyze all fMRI data.

Results: While down-regulating emotional responses (as assessed by subtracting the view from the decrease condition), the overall BD group compared to the HC group showed relatively less engagement of ventromedial, ventrolateral and dorsolateral prefrontal cortex (PFC) and dorsal anterior cingulate cortex ($p < 0.005$), especially while regulating responses to negative emotional stimuli. Additional state-related features were observed including reduced engagement in the rostral PFC in the elevated BD subgroup, while the depressed BD subgroup showed less engagement in ventral and dorsal anterior cingulate. In the preliminary analyses, compared to baseline, treatment with BE-SMART was associated with increases in ER-related engagement in the frontal regions that had shown the initial decreases in BD ($p < 0.05$).

Conclusions: Findings support deficits in frontal recruitment during attempts to down-regulate responses to emotional stimuli in BD, with some frontal patterns present across mood states suggesting they may be trait features of BD, and others that vary depending on mood state. Preliminary evidence supports a reversal of these functional deficits with the BE-SMART intervention suggesting that targeted psychobehavioral intervention can improve this frontal functioning.

Keywords: Bipolar Disorder, Emotional Regulation, Functional MRI (fMRI), Behavioral

Disclosure: Nothing to disclose.

W109. Resting State fMRI Network Changes in Major Depression Following Administration of Ketamine

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Background: Major depressive disorder (MDD) carries the heaviest burden of disability among mental and behavioral disorders according to the World Health Organization. Current drugs to treat MDD typically take several weeks to act and it is unclear which patients will respond to what drug. Ketamine has been found to be a rapid acting antidepressant, however not much is known about its mechanism of action. Mood improvement in patients is usually measured with one of several different rating scales none of which have been shown to have consistent neural correlates. For this study, a cohort of MDD patients each fMRI rest scan the course of a double-blind randomized placebo controlled cross-over ketamine infusion study: once at baseline, and before and after both placebo and drug infusions. Here we are interested in investigating the connectivity associations with mood improvement after ketamine in MDD.

Methods: 29 MDD subjects (ages 20-65, 17 female) are included in this analysis. Resting state fMRI scans were 8 minutes long with the subject's eyes closed (fMRI parameters: 3 T, TR:2.5 s, TE: 25 ms, FA: 90, res: 3.75x3.75x3.5 mm, matrix 64x64) along with a high resolution MPRAGE anatomical scan (1 mm isotropic). Cardiac and respiration data were also recorded. The data was preprocessed using AFNI3, motion and physiological noise corrected, blurred to 6 mm, filtered: bandpassed between 0.01 and 0.1 Hz, and aligned to the MNI 152 standard template. Network seeds were chosen from Raichle, 20114, and connectivity matrices and maps were created using 3dNetcorr at the individual level. Group level statistics were performed using 3dLME with the Montgomery-Asberg Depression Rating scale (MADRS) value and scan type as covariates.

Results: There was a significant main effect of MADRS score associated with changes in connectivity between the right and left prefrontal cortex regions and lateral parietal cortex. There was a significant interaction between scan type and MADRS score with connectivity changes between the insula and lateral parietal regions as well as thalamus and bilateral auditory cortex.

Conclusions: The connectivity changes found here reflect those found in the literature with respect to deficits found in MDD. They may help provide insight into the neural underpinnings of symptom profiles both before and after rapid-acting treatment with ketamine. Future work looking into connectivity fingerprinting of the individual subjects may reveal information about the heterogeneity of this MDD population.

Keywords: Ketamine, Major Depression Disorder, Functional MRI (fMRI), Resting State Functional Connectivity

Disclosure: Nothing to disclose.

W110. Nicotine Normalizes Cortico-Striatal Connectivity in Non-Smoking Individuals With Major Depressive Disorder

Abstract not included.

W111. A Pilot Study of Subcortical Shape and Lithium Response in Bipolar Disorder

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Background: Bipolar disorder is largely treatable, but the process of _x000C_finding the right medication for a given patient can take months to years. Lithium is a common fi_x000C_rst-line agent and identification of biomarkers that can reliably predict response is needed. The goal of this pilot project is to identify whether shapes of subcortical structures di_x000B_ffer between lithium responders and nonresponders.

Methods: Participants with bipolar I disorder (N = 12) were stabilized on lithium monotherapy and followed for up to two years to make a clinical determination of long-term response to treatment, after which they underwent MRI at 7 Tesla. Healthy comparison participants (N = 21) were group matched to cases on sex, age and education. Both males and females were included. Left and right amygdala and hippocampus were segmented semi-automatically. MRICloud created surface templates and calculated deformations to each patients' anatomy. A linear model was used to test for group differences in deformations at each vertex.

Results: Eight bipolar participants were classified as responders and four as non-responders. Permutation testing was used and group differences at each vertex with a FWER of 0.05 were considered significant. Vertices that significantly differed by response status were clustered in the posterior hippocampus and basomedial amygdaloid nucleus.

Conclusions: We identified alterations in shape of amygdala and hippocampus associated with long-term lithium response in bipolar disorder in one of the earliest subcortical shape analyses with 7 T imaging. These results may serve as candidate brain features for future studies examining potential biomarkers for treatment response.

Keywords: Lithium Response, Structural Neuroimaging, Bipolar Disorder

Disclosure: Nothing to disclose.

W112. Association of Neuroinflammation With Duration of Untreated Major Depressive Disorder

Abstract not included.

W113. Central Penetration and Receptor Occupancy in Human Brain by JNJ-55308942, a Selective Antagonist of the ATP-Gated P2X7 Receptor

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Background: P2X7 is an ATP-gated cation channel highly expressed on immune cells including brain microglia. Activation of the P2X7 receptor promotes the NLRP3 inflammasome assembly and release of neuroactive cytokines such as IL1β and IL-18. Over-activation of this pathway is hypothesized to play a role in the pathophysiology of mood disorders. In this study, we evaluated the occupancy of P2X7 in human brain by JNJ-55308942, a highly selective P2X7 antagonist. Occupancy was estimated by PET/MR using [18 F] JNJ-64413739, which had been previously qualified as a selective PET radioligand for the P2X7 receptor.

Methods: Single dose pharmacokinetics, safety, and tolerability of JNJ-55308942 were determined in a Phase 1 study and predictions of exposure/occupancy were developed from PET studies of rhesus macaque (data on file). Occupancy was tested in 6 healthy male subjects who underwent up to three PET scans with [18 F] JNJ-64413739. The first was a baseline scan and the other scans were acquired 4 h after up to 2 different oral doses of JNJ-55308942 (2 mg to 80 mg), given as an oral solution and following a standard breakfast. Subjects were positioned in the PET scanner (PETMR GE Signa) such that the entire brain volume was included in the field of view at one bed position. A T1 weighed volumetric MRI scan was acquired and a ZTE based MR scan for attenuation correction followed by acquisition of emission 3D list mode data over 90 minutes. Short MR sequences for motion correction were obtained at intermediate points. Arterial blood samples were obtained to define the input function and for radiometabolite analysis. Logan graphical analysis (LGA) was used to quantify tracer kinetics and to calculate regional volumes of distribution (VT) (PMOD v.3.7). Occupancy was estimated by analyzing baseline and post dose VT values using a Lassen plot.

Results: Single oral doses of JNJ-55308942 resulted in up to 79% occupancy across all brain regions, with apparent saturation of blocking by 40 mg. Tracer metabolism was not altered by pretreatment with JNJ-55308942. Adverse events were mild, and procedure related. There were no clinically significant changes in vital signs, ECG, or clinical labs.

Conclusions: Central penetration and engagement of the P2X7 receptor by JNJ-55308942 was confirmed and saturation of the target appears to occur by 40 mg. This information can assist in guiding dose selection of JNJ-55308942 for Phase 2 clinical trials, provide confidence that the hypothesis has been adequately tested, and optimize the safety margin. This study also confirms that [18 F] JNJ-64413739 is a suitable P2X7 PET ligand to guide early clinical evaluation of P2X7 antagonists.

Keywords: P2X7, Positron Emission Tomography Imaging, Receptor Occupancy, Human Clinical Trial

Disclosure: Janssen Pharma, Employe

W114. Endothelial Function is Differentially Associated With Brain Structure in Adolescents With Versus Without Bipolar Disorder

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Background: Endothelial dysfunction, a progenitor of atherosclerosis, is present among adults with mood disorders. It is not yet known whether EF is associated with brain structure among people with mood disorders. We therefore set out to investigate the association between EF and brain structure in adolescents with and without bipolar disorder (BD).

Methods: T1-weighted images of 42 BD adolescents and 53 psychiatrically healthy controls (HC) were acquired using 3T-MRI. FreeSurfer software was used to derive region of interest (ROI) volumes for: frontal lobe, prefrontal cortex (PFC), anterior cingulate cortex, hippocampus, and amygdala. Endothelial dysfunction was measured using pulse amplitude tonometry, yielding a reactive hyperemia index (RHI). General linear models examined the relation between ROI volumes and RHI, controlling for age,

sex, body mass index, and intracranial volume. Whole-brain vertex wise analysis was also conducted.

Results: There was a significant Group x RHI interaction effect on frontal lobe ($\eta p2 = 0.112$, $p = 0.001$), PFC ($\eta p2 = 0.079$, $p = 0.008$), and amygdala volumes ($\eta p2 = 0.057$, $p = 0.026$). In the HC group, RHI was significantly positively correlated with frontal lobe ($\eta p2 = 0.146$, $p = 0.007$) and approaching significance for PFC ($\eta p2 = 0.073$, $p = 0.064$). In contrast, there was a significant negative correlation between RHI and amygdala volume ($\eta p2 = 0.265$, $p = 0.001$) within the BD group. Whole brain analysis of RHI-cortical thickness correlations revealed 7 significant interaction clusters with peak vertices in bilateral precuneus, cuneus, and lateral orbitofrontal cortex; and left rostral middle frontal gyrus and right supramarginal gyrus. Analysis of RHI-cortical volume correlations revealed a significant interaction cluster with peak vertex in left inferior temporal gyrus.

Conclusions: Neurostructural-vascular reactivity associations may be anomalous among adolescents with BD. Future studies are warranted to examine additional neuroimaging phenotypes, and to evaluate putative underlying mechanisms.

Keywords: Bipolar Disorder, Structural MRI, Vascular, Adolescent

Disclosure: Nothing to disclose.

W115. Functional Connectivity, Cortical GABA and Neuroactive Steroids in Peripartum and Peripartum Depressed Women

Abstract not included.

W116. Functional Biomarkers of Remitted Psychotic Depression

Abstract not included.

W117. Adolescent Markers of Depression

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Background: One in five teens suffer from major depression before they reach adulthood. Early identification of adolescents at risk for depression is critical to prevention efforts. Adults with depression show smaller volumes of the amygdala, orbitofrontal cortex, anterior cingulate cortex, and hippocampus, yet larger volumes of the cerebellum and lateral ventricle. Whether these neural features are present in adolescents with depression, or develop after years of depression, is unclear. The National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) provides an ideal design to longitudinally study these neural features in adolescents who develop depressive symptoms during the study compared to non-affected peers. The NCANDA cohort consists of 831 youth initially assessed at ages 12-21 years, half at elevated risk for mental health and/or substance use during adolescence, who are followed annually.

Methods: In the NCANDA cohort, we prospectively examined whether risk factors could be identified for predicting major depression based on DSM-IV criteria in a subgroup of healthy adolescents ($n = 643$). We used machine learning to do so on the basis of structural and diffusion tensor neuroimaging markers at baseline. We hypothesized that subsequently depressed adolescents and young adults, compared to continuously healthy youth, would exhibit differences in structural magnetic resonance imaging (MRI) data, specifically smaller volumes of the orbitofrontal cortex, amygdala, anterior cingulate cortex, hippocampus, and basal ganglia.

Results: We identified 22 neuroimaging features that were more most predictive of transition from healthy to a depressed state in adolescents using a machine learning approach, with a specificity of 0.60 and sensitivity of 0.54 using 10-fold cross-validation. Thicknesses and volumes were found to be decreased in several of these regions in depressed subjects compared to non-depressed subjects after a transition from a non-depressed baseline, consistent with lesser brain maturation and supporting our hypothesis.

Conclusions: We identified neuroimaging metrics as risk factors for predicting major depression in healthy adolescents. Future directions include examining these relationships using other techniques including linear statistical models. The results may point to neural systems that could be explored as targets of earlier interventions and preventative measures to reduce the incidence of depression and increase the percentages of individuals who engage in treatment in this population in the future.

Keywords: Adolescent Depression, Machine Learning, Neuroimaging Biomarkers

Disclosure: Nothing to disclose.

W118. Serum Cortisol Levels and the Cortical Thinning Hypocampal Volume, and White Matter Integrity in Major Depression

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Background: Higher morning cortisol levels was reported in a subgroup of major depressive disorder (MDD). Higher cortisol levels may be due to a dysregulation of hypothalamic–pituitary–adrenal axis. We investigated the relationship between cortical thinning or white matter integrity and serum cortisol levels in MDD patients with the first depressive episode and drug-naive using an automated surface-based morphometry (SBM) method and a tract-based spatial statistics (TBSS) method. We also investigated volume -based connectome analysis in the MDD patients.

Methods: The study was approved by the ethical review board of our university. The MR imaging data were obtained using a 3T scanner by a three-dimensional fast-spoiled gradient recalled acquisition with steady state. Thirty drug-naive patients with MDD and 41 age- and gender matched healthy subjects (controls) were enrolled. We used the SBM method (Freesurfer) to generate cortical thickness maps and measured the cortical thickness in each subject. The both groups performed diffusion tensor imaging (DTI) scans and an analysis was conducted using TBSS. Morning blood samples were collected from all participants for cortisol measurements. Also, volume-based connectome was performed in the MDD patients and controls.

Results: 1)The serum cortisol levels were significantly higher in the MDD patients than in the controls. 2)The MDD patients were significant thinner of the left lateral orbitofrontal cortex than controls. 3)A significant negative correlation was found between the thickness of the left lateral orbitofrontal cortex and the serum cortisol levels in the MDD patients. 4)The MDD group had significantly decreased FA values in the inferior fronto-occipital fasciculus, uncinate fasciculus and anterior thalamic radiation. 5)A significant negative correlations were observed between the FA values of the inferior fronto-occipital fasciculus, uncinate fasciculus

and anterior thalamic radiation and the serum cortisol levels in the MDD group. 6)The connective impairment between orbitofrontal cortex and hippocampus was found in the MDD patients with melancholic features.

Conclusions: The thickness of the lateral orbitofrontal cortex was significantly decreased in the MDD patients, which was associated the serum hypercortisolemia. The impaired white matter integrity of the brain was also associated with hypercortisolemia. Furthermore, volume-based connectome reinforced the evidence of the disturbance in and frontal–limbic connectivity in the MDD patients.

Keywords: Cortical Thinning, White Matter Integrity, Hippocampal Shape, Cortisol, Major Depression

Disclosure: Nothing to disclose.

W119. Brain Changes With an Emotion Regulation System Targeted Psychobehavioral Intervention

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Background: Non-medication therapies are critically-needed to treat impaired emotional regulation, which affects millions of individuals worldwide, causes immeasurable suffering, disability, and can be central to suicide. Emotional dysregulation is extreme in bipolar disorder for which the treatment needs are pressing, especially in adolescents and young adults, as improving emotional regulation may not only reduce acute symptoms, but prevent disease progression, improve prognosis, and decrease risk of suicide. We are studying a promising novel psychobehavioral intervention, Brain Emotion Self-Monitoring and Regulation Therapy (BE-SMART), designed to target emotional regulation problems and their underlying brain circuitry.

Methods: Adolescents and young adults with bipolar disorder (ages 16-24 years) participated in a psychobehavioral Brain Emotion SelfMonitoring and Regulation Therapy (BE-SMART) intervention designed to target the functioning of the brain circuitry that subserves emotional regulation. This adjunctive intervention consisted of training in and practicing healthy behaviors to improve emotion regulation over 12 weeks, including 3 in-person visits and the remainder conducted via secure videotelecommunication. Clinical, behavioral and functional magnetic resonance imaging (fMRI) data were obtained before the intervention ("pre"), at the end of 6 weeks ("mid") and following 12 weeks ("post"). During scans, subjects participated in an event-related task in which they viewed faces depicting fearful, happy, or neutral expressions and were instructed to press a button to make a male-female determination. Statistical Parametric Mapping (SPM12) software was used to preprocess and analyze fMRI data.

Results: Preliminary data for 10 subjects show hypothesized pre to post decreases in amygdala and increases in ventral prefrontal cortex ($p < 0.001$). Similar changes from pre to mid were observed that were less robust. Brain changes with the intervention paralleled improvements in depression (Hamilton Depression Rating Scale), mania (Young Mania Rating Scale), emotional reactivity (Emotion Reactivity Scale) and regulation of emotions (Difficulties in Emotion Regulation negative and positive versions).

Conclusions: The findings provide preliminary evidence for beneficial effects of a targeted psychobehavioral intervention on emotion regulation and the brain circuitry that subserves it.

Keywords: Bipolar Disorder, Functional MRI (fMRI), Behavioral, Emotional Regulation

Disclosure: Aetna, Honoraria

W120. Selective Volume Increase in the Dentate Gyrus in Depressed Patients Receiving Electroconvulsive Therapy as Measured With 7 Tesla MRI

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Background: Electroconvulsive therapy (ECT) is the most effective treatment for depression, yet its working mechanism remains unclear. In the animal analogue of ECT, neurogenesis in the dentate gyrus (DG) of the hippocampus has been observed. In humans, volume increase of the hippocampus has been observed. If this volume increase is attributable to neurogenesis, it is expected to be exclusively present in the DG, while other processes like angiogenesis and synaptogenesis will also affect other hippocampal subfields. 7 tesla MRI can accurately delineate different subfields and investigate whether volume increase is uniquely present in DG.

Methods: In total, thirty-eight participants (12 healthy controls, 26 patients with severe depression) were scanned twice on a 7 T scanner. SmartExam planning was used to Ensure exact similar placement on the two occasions. Patients had 10 sessions of bilateral ECT between the two scan sessions. Hippocampi were investigated using Automated Segmentation of Hippocampal Subfields (ASHS) pipeline, FSL (5.0.9) and ANTs tools.

Results: Here we show that in depressed patients, a significant increase in DG volume was observed after ECT ($p < 0.0001$), while other hippocampal subfields were unaffected. (all $p > 0.05$). Baseline DG volume (together with age and gender) predicted clinical effect ($R2 = 0.48$, $p = 0.04$, and increase in DG volume was associated with clinical effect ($R2 = .71$, $p = 0.0003$).

Conclusions: These findings strongly suggest that ECT induces neurogenesis in the DG in depression.

Keywords: Electroconvulsive Therapy, Hippocampal Subfields, Predictor of Treatment Response

Disclosure: Scientific Adviser to Gabather, Consultant

W121. Adolescent Stress-Induced Dysregulation of HPA Axis: Relevance to Postpartum Mood Disorders

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Background: Mood disturbance and cognitive impairment during the postpartum period are common and serious problems in women's mental health. Early life stress, including adolescent psychological stress, increases the risk for such postpartum emotional and cognitive problems. Nonetheless, the mechanisms by which psychological stress before pregnancy influences postpartum mood and cognition are poorly understood. In the present study, we have built a novel platform to study the biological mechanisms underlying the effects of adolescent stress on postpartum emotional and cognitive behaviors in first-time mothers, based on the adolescent social isolation paradigm we have previously published. We also examined how history of major mental illnesses before pregnancy affects the hypothalamic-pituitary-adrenal (HPA) axis and postpartum mental conditions in humans.

Methods: Healthy virgin C57BL/6 J female mice were exposed to mild isolation stress during late adolescence (from 5 to 8 weeks of age), which alone caused no endocrine or behavioral changes. Each mouse was then mated with a C57BL/6 J male and gave birth to pups. Behavioral tests and measurement of hormone levels in plasma were performed at 0-week, 1-week, and 3-week postpartum. Dams were treated with a glucocorticoid receptor antagonist from gestation day 14 to 1-week postpartum. Human cortisol levels in plasma from participants with a history of major mental illness before pregnancy were examined at 2nd trimester, 3rd trimester, 2-week postpartum, and 6-week postpartum.

Results: We observed behavioral deficits in tail suspension/forced swim (mood) and three-chamber social interaction (social cognition) tests at one-week postpartum, but not immediately after delivery, in dams exposed to adolescent stress. The stressed dams displayed sustained elevation of plasma corticosterone (glucocorticoids in rodents) by disturbance of negative feedback of the HPA axis after delivery, concurrent with the emergence of behavioral deficits related to mood and social cognition at one week postpartum. The sustained elevation of corticosterone and behavioral deficits in stressed dams lasted at least three weeks postpartum. The behavioral deficits in stressed dams were ameliorated by administration of a glucocorticoid receptor antagonist, suggesting that the aberrantly sustained elevation of glucocorticoids during the postpartum period could underlie the postpartum behavioral deficits related to mood and social cognition. Patients who have a history of mental illness before pregnancy and were diagnosed with a mood disorder during the postpartum period showed sustained elevation of plasma cortisol (glucocorticoids in humans), like our stressed postpartum dams, in comparison to participants with no history and participants with history and no mental deficits during the postpartum period.

Conclusions: Our mouse study provides biological insights into how pre-partum psychosocial stress can lead to enduring physiological effects that may influence behaviors in the developmental trajectory from adolescence to the postpartum period. We also showed the significance of vulnerability, including history of mental illnesses, on regulation of HPA axis and mental deficits during the postpartum period in human subjects. These findings will have a broad impact on the well-being of mothers, their children, and the rest of the family.

Keywords: Adolescent Stress, HPA Axis, Postpartum, Mood, Social Cognition

Disclosure: Nothing to disclose.

W122. Higher Testosterone Levels are Associated With Depressive Symptoms in Overweight Premenopausal Women

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Background: Large epidemiologic studies and meta-analyses (Luppino et al., 2010; Zhao et al., 2009) support an association between obesity and depression, which appears to be stronger in women than in men. Given the observed sex differences in both adipose fat accumulation and depression prevalence, it is likely that sex hormones substantially influence the interplay between obesity and depression in women. What remains unclear is whether and how sex hormone levels impact the relation between weight status and depressive symptoms in overweight individuals. Here, we investigated whether a potential relation between increased body mass index (BMI) and depressed mood might be mediated by sex hormone levels in a large, population-based, cross-sectional study. To this end, we investigated 1. the association of being overweight with being depressed, and 2. the role of estradiol, total testosterone, and sex hormone-binding globulin levels in relation to being overweight and being depressed in a large cross-sectional study.

Methods: We included a total of 3124 women, 970 premenopausal and 2154 postmenopausal, from the Leipzig Research Centre for Civilization Diseases (LIFE) Adult study in our analyses. We evaluated cross-sectional associations between being overweight (BMI > 25 kg/m2), serum levels of sex hormones, and depressive symptomatology according to CES-D (Centre for Epidemiologic Studies Depression) scores by logistic regression analyses and explored a potential mediation of the relation between weight and depression by sex hormone levels.

Results: Being overweight was significantly associated with depressive symptoms in premenopausal (OR = 1.66, CI = 1.03-2.65, p = 0.036), but not in postmenopausal women (OR = 1.06, CI = 0.71-1.57, p = 0.796). Overweight women had higher free testosterone levels compared with normal weight women in both premenopausal (12.8 ± 8.3 vs. 8.9 ± 6.1 pmol/l, $p < 0.001$) and postmenopausal (10.6 ± 7.5 vs. 7.5 ± 5.6 pmol/l, $p < 0.001$) groups. Premenopausal women with depressive symptomatology (CES-D ≥ 23 points) had higher free testosterone levels compared to women with a normal CES-D score (13 ± 8 vs. 9 ± 6 pmol/l, $p < 0.001$). We found a small but significant mediation effect of the relation between weight and depression in premenopausal women through free testosterone levels (OR = 1.03, p = 0.022).

Conclusions: Our findings support that being overweight, as well as depressed, is associated with higher free testosterone levels in premenopausal women. Based on these cross-sectional data, we conceptualize a model of how sex hormone levels can be integrated in a risk model for depression in overweight women during their reproductive years: Free testosterone levels might be one of the mediating factors of depression in overweight premenopausal women. Future longitudinal studies are needed to confirm this model. As functional hyperandrogenic states associated with increased abdominal fat accumulation have been shown to be reversible with weight loss, our findings emphasize the importance of maintaining a healthy body weight for women in early adult and midlife for effective treatment, and possibly prevention of depression. Based on this insight, pharmacological approaches targeting androgen levels in overweight depressed females, in particular when standard anti-depressive treatments fail, could be of specific clinical relevance.

Keywords: Depression, Obesity, Sex Hormones

Disclosure: Nothing to disclose.

W123. The Priori Emotion Dataset: Linking Mood Assessments to Emotion Detected In-The-Wild From Speech Segments Recorded on a Mobile Device

Abstract not included.

W124. Sympathetic Nervous System Activity, Intestinal Permeability, and Innate Immunity in Adolescent Depression

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Background: Inflammation causes "sickness behavior" in animals. In humans, major depressive disorder (MDD) has been associated

with low-grade inflammation. While obesity, chronic illness, smoking, are some factors that can trigger an inflammatory response, chronic mild stress is associated with the release of damage-associated molecular patterns, which trigger activation of inflammasomes, which induce an innate immune response. Importantly, microbial-associated molecular patterns potentiates the activation of inflammasomes, highlighting the role of non-pathogenic commensal gut bacteria in this process.

As such, this study sought to examine the association between the sympathetic nervous system (SNS), intestinal permeability promoting the translocation of bacterial antigens, and innate immunity in adolescent depression.

Methods: Medically-healthy 12 to 17-year-old unmedicated female participants with MDD and healthy controls were enrolled. They underwent a diagnostic evaluation following the DSM-5 and the Child Depression Rating Scale-Revised (CDRS-R) was completed. Pre-ejection period (PEP), a marker of SNS activity, was collected at rest and analyzed, using a MindWare system. Following an overnight fast, participants ingested lactulose and mannitol and collected urine for 4 h while still fasting. The lactulose to mannitol ratio (LMR) was computed using the fractional excretion of each sugar. A blood draw was obtained to measure interleukin 1β (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor α (TNFα) concentrations. Correlational analyses were used to analyze the data.

Results: Forty-one participants (age: 14.8 ± 1.6 years, $n = 25$ with MDD) were enrolled. PEP was inversely associated with neurovegetative symptom severity on the CDRS-R ($r = -0.31$, $p < 0.06$, $n = 37$). In the 30 participants with gut permeability data, LMR was significantly associated with depression severity, particularly neurovegetative symptom severity ($r = 0.37$, $p < 0.05$). Notably, the association between neurovegetative symptom severity and PEP was substantially reduced after adjusting for LMR. Depression severity was also associated with circulating cytokines (r for IL-1β = 0.43, $p < 0.05$; for IL-6 = 0.30, $p > 0.10$; and for TNFα = 0.40, $p < 0.06$, $n = 25$).

Conclusions: This is the first study to examine gut permeability in unmedicated adolescents, offering preliminary support for a mechanistic pathway linking SNS activation to increased gut permeability and activation of the innate immune system, contributing to the emergence of neurovegetative symptoms of depression.

Keywords: Adolescent Depression, Depression Inflammation Cytokine, Sympathetic Nervous System, Intestinal Microbiome

Disclosure: Nothing to disclose.

W125. Semi-Supervised Machine Learning Reveals 3 Patterns of Cognitive Function in Depressed Youth

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Background: Depression is a common psychiatric illness and among the leading causes of disability worldwide. Depression often begins in adolescence, with an estimated 1-year prevalence of 4-5% and increasing rates of suicide. As with adults, there is heterogeneity in treatment response and longitudinal prognosis in youth. Increasingly, it is recognized that biological heterogeneity is a likely source of variability in outcomes. Prior work in adults has used machine-learning tools to parse heterogeneity and define subtypes that are not apparent on clinical presentation alone. We used a recently developed semi-supervised machine learning method to identify cognitive subtypes in a large sample of depressed youth.

Methods: Participants were drawn from the Philadelphia Neurodevelopmental Cohort, a community-based sample of youth ages 8-21. Cognitive and psychiatric phenotypes were obtained on a sample of $n = 9{,}498$. The present study considered 712 youth (mean age: 16.1 years, 67% female) who met screening criteria for major depressive disorder, and an equal number of typically developing (TD) youth who screened negative for a history of significant psychopathology and who were matched on both age and sex (total $n = 1{,}424$). Cognition was assessed using the Penn Computerized Neurocognitive Battery, which measured performance accuracy and speed on 12 cognitive domains and speed on two additional domains. To find subtypes of depression, we used a semi-supervised machine-learning algorithm called HYDRA (Heterogeneity through Discriminative Analysis). HYDRA reveals homogenous subtypes within a clinical group by simultaneously maximizing subtype-specific margins between patient clusters and controls, while adjusting for covariates (in this case: age and sex) and determining cluster memberships. Cross-validation clustering stability was evaluated over a resolution range of 2-10 clusters, as quantified by the adjusted rand index (ARI). Post-hoc multiple regression analyses were performed to determine cognitive differences driving the clustering results. Additionally, subtypes were evaluated for clinical differences using summary scores from a previously published bifactor analysis of psychopathology data from the structured clinical interview. As this clinical data was not used in the clustering procedure, it provides an independent validation of each subtype's clinical characteristics. In all analyses of cognitive scores and clinical factors scores, we accounted for multiple comparisons using the False Discovery Rate ($Q < 0.05$).

Results: Of the 10 clustering solutions evaluated, the highest ARI was present at the 3-cluster solution (including 3 depressed subtypes and the typically-developing control group). There were no differences in age ($p = 0.78$) or sex ($p = 0.13$) between subtypes, but maternal education was lower and the percentage of non-Caucasians was higher in Cluster 2 (both $p < 0.001$). Analysis of cognitive data revealed that clusters were significantly different across all 26 cognitive measures, with the strongest differences in nonverbal reasoning accuracy ($F = 128.62$, P[fdr] = 2.85 x 10^-72), verbal reasoning accuracy ($F = 76.14$, P[fdr] = 1.50 x 10^-44), and emotion recognition speed ($F = 70.30$, P[fdr] = 1.91 x 10^-41). Overall, Cluster 1 had better performance than TD comparators across many cognitive tasks (high accuracy, moderate speed), whereas Cluster 2 was cognitively impaired (low accuracy and low speed). Finally, Cluster 3 was impulsive, with both low accuracy and high speed.

When the clinical features of depression subtypes were evaluated using the scores from the bifactor analysis of the clinical interview, a convergent pattern emerged. As expected, all depressed subtypes had higher levels of psychopathology. In pairwise between-cluster analyses, Clusters 1 and 3 were not significantly different from each other in measures of clinical psychopathology. However, Cluster 2 had significantly more psychosis, externalizing, and fear symptoms than other subtypes. The strongest pairwise differences between Cluster 2 and the other clusters were in fear symptoms (both P[fdr] < 0.001).

Conclusions: This study utilized a recently developed semi-supervised machine learning method to reveal cognitive heterogeneity in depressed youth. Subtypes included those with cognitive impairment and an elevated symptom burden, an impulsivity subtype, and a group of youth whose cognitive functioning was spared despite their substantial symptomatology. Ongoing efforts will link these subtypes to disruptions of brain networks in the sub-sample of youth who completed multi-modal neuroimaging.

Keywords: Machine Learning, Adolescent Depression, Cognitive Subtypes, Mood Disorder Subtypes, Major Depression Disorder

Disclosure: Nothing to disclose.

W126. The (Sub-) Acute and Persisting Effects of Psilocybin on Creativity, Empathy and Satisfaction With Life in Two Settings

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Background: Research into the therapeutic potential of psychedelics has re-emerged and (preliminary) findings are promising. Depression and anxiety disorders are amongst the disorders of focus and symptoms seem to be resolved with a single dose of a classical psychedelic, psilocybin. The cognitive mechanism behind this effect and the longevity of it is not yet clear. While both psychopathologies are characterized by cognitive rigidity, disturbed empathy, and lower satisfaction with life our aim was to investigate whether psilocybin can change and improve this behavior acutely and with a longer duration. To that end, two studies assessing these effects in a naturalistic and laboratory setting were conducted.

Methods: In Study 1 the effect of psilocybin was assessed on performance of volunteers of both sexes (age $M = 34.8$, $SD = 8.9$) attending a psilocybin retreat at baseline ($N = 53$) and the morning after use ($N = 41$), and 7 days after use ($N = 22$) via an online application. Only volunteers who completed the tasks at the three test moments were included in the statistical analysis (GLM Repeated Measures ANOVA; Time (3 levels)).

Study 2 was conducted according to a placebo-controlled, double-blind, mixed design with Treatment (2 levels, psilocybin 0.17 mg/kg, placebo) as between-subject factor and Time of Testing (2 levels, 118'-138' and 7 days post-treatment) as within-subject factor. Participants ($N = 30$; age $M = 23.6$, $SD = 3.0$) were healthy volunteers of both sexes with experience with psychedelics.

Parallel versions of the Picture Concept Test (PCT) were used on each testday to assess convergent thinking (number of correct associations) and divergent thinking (fluency of alternative associations, originality, and their ratio). The Multifaceted Empathy Test (MET) was used to assess cognitive empathy (number of correct recognized emotions) and emotional empathy (level of concern and arousal). The Satisfaction with Life Questionnaire was used to assess the cognitive component of mental wellbeing and in study 2 a visual analogue scale (VAS) was administered repeatedly to assess whether participants felt affected by psilocybin.

Both studies were approved by an ethics committee (Maastricht University) and performed in accordance with the Helsinki Declaration.

Results: Study 1. GLM RM ANOVA of the PCT revealed a main effect of Time on convergent thinking ($F(2,28) = 6.58$, $p = .005$) and two parameters of divergent thinking, Fluency ($F(2,26) = 3.58$, $p = .04$) and Originality ($F(2,26) = 3.37$, $p = .05$). The former effect on convergent thinking indicated that relative to baseline, the number of correct answers was statistically significant higher 1 week after the psilocybin experience ($p = .02$). The latter effect demonstrated that, compared to baseline, a higher number ($p = .01$) and more original answers ($p = .02$) were generated the day after the experience, whereas one week later divergent thinking had returned to baseline.

With respect to empathy, ANOVA showed that ratings of arousal were elevated ($F(2,26) = 7.70$, $p = .002$) the morning after the experience ($p = .002$) and this effect persisted for 7 days ($p = .05$). There was no Time effect on cognitive empathy; the psilocybin experience did not affect the ability to recognize emotions.

Analysis revealed a main effect of Time on Satisfaction with Life ($F(2,28) = 9.81$, $p = .001$); satisfaction was rated significantly higher (satisfied) the morning after the experience ($p = .05$) and this effect persisted for 7 days ($p = .002$), compared to baseline (slightly satisfied).

Study 2. There were no statistically significant baseline differences in performance or satisfaction with life between the two treatment groups.

GLM RM ANOVA of the PCT revealed a main effect of Time ($F(1,26) = 18.20$, $p < .001$), Group ($F(1,26) = 4.38$; $p = .05$), and their interaction ($F(1) = 6.55$; $p = .02$) on convergent thinking; 118' post-treatment, the number of correct answers was lower in the group having received psilocybin compared to the placebo group. This performance difference between groups was absent 7 days post-treatment. Additionally, there was a main Time effect on two parameters of divergent thinking, Fluency ($F(1,25) = 13.7$, $p = .001$) and Ratio ($F(1,25) = 8.15$, $p = .009$); the number of generated associations was higher 7 days post-treatment, however, when originality was taken into account, a decrease in ratio ('true divergent thinking') was shown; there was no Time effect on Originality and there were no effects of Treatment or Time by Treatment on divergent thinking. There were no effects of Time, Treatment or their interaction on empathy parameters or satisfaction with life ratings. A main effect of Treatment ($F(1,28) = 89.2$), $p < .001$) was shown on the VAS demonstrating that the psilocybin effect was experienced significantly more in the group who received psilocybin compared to the placebo group; the intensity was rated as being comparable to previous experiences.

Conclusions: Persisting effects of psilocybin were only assessed when psilocybin was taken in a social setting with satisfaction with life and emotional empathy being increased up to 7 days after the experience. There were no persisting effects on creative thinking, though, when taken in a social setting convergent thinking was enhanced 7 days post-experience compared to baseline. Current findings emphasize the importance to assess psilocybin effects in different settings, with different doses and times post-dosing, and with a range of objective and subjective parameters.

Keywords: Psilocybin, Creativity, Empathy, Wellbeing, Psychedelic Medicine

Disclosure: Study 2 was co-financed by the Beckley Foundation, Grant

W127. Benzodiazepine Concomitant Medication Attenuates Antidepressant Effect of Ketamine

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Background: Fast antidepressant effect of ketamine has become a breakthrough in the research and treatment of depression. Concerning GABA neurotransmission being a shared target for both ketamine and benzodiazepines (BZD), we evaluated the influence of BZD on the antidepressant effect of single ketamine infusion in depressed patients.

Methods: Data from 47 patients (27 females) with major depression (MADRS ≥ 20, ≥ 1 prior non-response to antidepressant treatment in current episode, stable dose of antidepressants at least 4 weeks prior to admission) entered the analysis. All subjects were given infusion of subanesthetic dose of racemic ketamine (0,54 mg per kg) as an add-on medication to previous depression treatment.

Results: Thirteen patients (28%) reached ≥ 50% reduction in MADRS. Nineteen (40%) patients took concomitant benzodiazepines. The doses of BZDs were significantly higher in non-responders ($p = 0.007$). ROC analysis distinguished responders from non-responders by criterion of > 8 mg of DZ equi (BZD +) with a sensitivity of 80% and a specificity of 84.6% ($p<0.001$). RM-ANOVA revealed different time pattern of response to ketamine between BZD + and BZD- (≤ 8 mg of DZ equi) group, with comparable decrease of depressive symptoms after 24 h after infusion, but significantly better outcome in BZD + in day 3 ($p = 0.04$) and day 7 ($p = 0.02$).

Conclusions: Concomitant benzodiazepine treatment attenuates ketamine´s antidepressant effect. The pathophysiological, clinical and methodological implications of this finding should be considered in future research design and ketamine treatment.

This work was supported by AZV (MZCR) grants 15-29370 A, 15-34524 A, 16-29857 A and NV18-04-00260.

Keywords: Ketamine, Major Depressive Disorder (MDD), Benzodiazepines

Disclosure: Nothing to disclose.

W128. Propofol for Treatment-Resistant Depression: A Pilot Study

Abstract not included.

W129. Lithium Versus Other Mood Stabilizers in a Longitudinal Study of Bipolar Youth

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Background: Lithium is the mainstay for treatment of bipolar disorder (BD) in adults, and numerous studies have shown it to be more effective than other mood stabilizers on a population level. However, the evidence in youth has been much more limited. While one randomized controlled trial showed that lithium was a helpful treatment for mania in children and adolescents, a large, multi-site RCT found it to be inferior to risperidone for the treatment of mania. There is also a dearth of studies assessing longer-term effects of lithium treatment, particularly in the pediatric population. We used longitudinal, observational data from the Course and Outcome of Bipolar Youth (COBY) study to assess whether lithium (vs. other mood stabilizers) was associated with improved outcomes, including mood symptoms, suicidality, and functioning.

Methods: COBY is an ongoing longitudinal study of 413 youth, age 7-17 years old at the time of recruitment, who had BD I, BD-II, or subthreshold BD; they have been followed biannually for up to 15 years. The Adolescent Longitudinal Interval Follow-Up Evaluation (A-LIFE) was used to assess medication exposure, mood symptoms, and psychosocial function over the preceding follow-up period. Suicide items from the K-SADS Depression Rating Scale (DEP-P; rating worst week over the past month) were also utilized. To assess the relationship between medication and outcomes, we compared follow-up periods where the participant reported taking lithium > 75% of the time (LI) vs. blocks where the participant reported taking another mood stabilizer (e.g. atypical antipsychotic, lamotrigine, valproic acid, but not lithium) > 75% of the time (OTHER MS). Individuals on both lithium and another mood stabilizer were classified as LI. We used mixed models (implemented in SAS 9.4) to assess whether LI vs. OTHER MS periods differed according to depressive symptoms, manic symptoms, suicidality, psychosocial function (clustering within individual). We used Lasso penalized regression (implemented in R) to optimally adjust for baseline covariates; sensitivity analyses were conducted to further adjust for time-varying covariates (which have complex relationships with both exposure and outcome) and to assess relationships in youth (< 18 years old). In a smaller sample of participants who did not take lithium during the first follow-up period, we assessed predictors of later lithium exposure.

Results: A total of 340 participants contributed 2610 follow-up periods (874 LI, 1736 OTHER MS). Compared to OTHER MS, the LI group was slightly older and had an older age of BD onset ($p < .05$). After adjusting for demographic variables, the LI group (vs. OTHER MS) had fewer suicide attempts (OR = .51; 95% CI = .28, .95; $p = .03$), fewer depressive symptoms on a 6 point scale ($\beta = -.19$; 95% CI = -.32, -.06; $p = .004$), and fewer psychosocial difficulties on a 16 point scale ($\beta = --.55$; 95% CI = -.90, -.19; $p = .003$). There were no differences in manic symptoms, and a trend toward the LI group experiencing more manic symptoms than the OTHER MS group ($p = .09$). Adjusting for additional clinical variables (lifetime hospitalizations, lifetime psychosis, and comorbidity) did not change these findings. Similar findings were observed in the subgroup of participants < 18 years old at the time of visit, and age*medication interactions were not significant. In a sample not exposed to lithium during the first six-month follow-up period, those who were later prescribed lithium (24/216) had higher rates of suicidality (OR = 2.6; 95% CI = 1.08,6.31; $p = .04$) and mania (OR = 2.4; 1.00, 5.59) prior to lithium exposure. Thus, the finding that LI vs. OMS is associated with fewer suicide attempts is unlikely to be attributable to (and is likely underestimated due to) confounding by indication.

Conclusions: There are significant limitations when assessing medication use in observational data; these include confounding by indication, exposure misclassification, and missing data. However, observational studies also have advantages such as duration of follow-up and generalizability. Our findings are consistent with studies in adult populations, showing that lithium (compared to other mood stabilizers) is associated with decreased suicidality, less depression, and better psychosocial functioning. Given the paucity of evidence regarding lithium in children and adolescents, these findings have important clinical implications for the pharmacological management of youth with BD.

Keywords: Bipolar Disorder, Lithium, Child and Adolescent Psychiatry

Disclosure: Nothing to disclose.

W130. Cariprazine Efficacy in Bipolar I Depression With and Without Concurrent Manic Symptoms: Post Hoc Analysis of 3 Randomized, Placebo-Controlled Studies

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Background: Mixed affective states are defined by the simultaneous occurrence of depressive and manic symptoms. Compared with a depressive or manic episode without symptoms from the opposite pole, bipolar depression with manic symptoms is associated with more severe symptoms, higher rates of mood episode recurrence and comorbidities, worse clinical outcomes, lower rates of treatment response, and increased risk of suicidality. Antidepressants, although commonly used, have weak evidence of efficacy and may increase the risk of switching to a manic

episode. Cariprazine is a dopamine D3-preferring D3/D2 receptor partial agonist and 5-HT1A receptor partial agonist, with demonstrated dopamine D3 receptor-dependent antidepressant-like effects in animal models. It is FDA approved for the treatment of adults with schizophrenia (1.5-6 mg/d) and manic or mixed episodes associated with bipolar I disorder (3-6 mg/d); cariprazine is also in development as monotherapy in bipolar depression and as adjunctive treatment in major depressive disorder. In 3 phase II/III, randomized, double-blind, placebo-controlled trials in patients with bipolar depression, cariprazine 1.5 mg/d demonstrated efficacy versus placebo in improving depressive symptoms. Post hoc analyses were conducted on data from these 3 positive studies to evaluate the subset of patients with bipolar depression and concurrent manic symptoms.

Methods: Patients included in the constituent studies met DSM-IV-TR or DSM-5 criteria for bipolar I disorder with a current major depressive episode; clinical inclusion criteria included a Hamilton Depression Rating Scale total score ≥ 20 and Young Mania Rating Scale (YMRS) total score ≤ 10 (1 study) or ≤ 12 (2 studies). Patients with and without concurrent manic symptoms were identified by baseline YMRS total scores of ≥ 4 and < 4, respectively. Efficacy was assessed in cariprazine 1.5 mg/d and 3.0 mg/d dose groups versus placebo. Outcomes included least squares mean change from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total and individual item scores analyzed using a mixed-effects model for repeated measures in the intent-to-treat population. MADRS response (≥ 50% improvement) and remission (total score ≤ 10) rates were analyzed using the last observation carried forward.

Results: Of 1383 patients with bipolar depression randomized to treatment, 808 (58.4%) had concurrent manic symptoms (placebo = 262; cariprazine: 1.5 mg/d = 275, 3.0 mg/d = 271) and 575 (41.6%) did not (placebo = 198; cariprazine: 1.5 mg/d = 186, 3.0 mg/d = 191). For patients with concurrent manic symptoms, mean reduction in MADRS total score from baseline to week 6 was significantly greater for both the cariprazine 1.5 mg/d and 3.0 mg/d groups compared with placebo, with least squares mean differences (LSMDs) of -2.5 (P = .0033) and -2.9 (P = .0010), respectively; for patients without manic symptoms, the LSMD was significant for the 1.5 mg/d dose (-3.3; P = .0008), but not for the 3.0 mg/d dose (-1.9, P = .0562). In patients with manic symptoms, the LSMDs were statistically significant versus placebo for cariprazine 1.5 mg/d and 3.0 mg/d on 5 MADRS individual items: Apparent Sadness, Reported Sadness, Reduced Appetite, Concentration Difficulties, and Lassitude (P < .05 each dose, each item); on the Inner Tension item, the LSMD versus placebo was only significant for the 1.5 mg/d dose (P < .05). In patients without manic symptoms, the 1.5 mg/d dose was significantly different versus placebo (P < .05) on all items except Inner tension and Suicidal Thoughts; 3.0 mg/d was only significantly different versus placebo on Apparent Sadness and Inability to Feel (P < .05). The percentage of patients with concurrent manic symptoms who met response criteria was significantly greater for cariprazine 1.5 mg/d (46.6%, P = .0402) and 3.0 mg/d (49.8%, P = .0052) than for placebo (37.8%). The percentage of patients with manic symptoms meeting remission criteria was also significantly greater for cariprazine 1.5 mg/d (31.3%, P = .0064) and 3.0 mg/d (31.4%, P = .0055, than for placebo (21.0%). In patients without manic symptoms, cariprazine 1.5 mg/d had significantly higher rates of response (45.2%, P = .0156) and remission (32.3%, P = .0074) versus placebo (33.3% and 20.7%, respectively); for 3.0 mg/d, rates of response (41.9%, P = .0655) and remission (25.1%, P = .2207) were not significant versus placebo (33.3% and 20.7%, respectively).

Conclusions: In a post hoc analysis of data from patients with bipolar depression and concurrent manic symptoms, significant improvement in depressive symptoms was demonstrated for cariprazine versus placebo across a range of depressive symptoms. Cariprazine 1.5 and 3.0 mg/d doses were consistently effective in patients with depression and manic symptoms, while only the 1.5 mg dose was consistently more effective than placebo in patients without manic symptoms. These results suggest that cariprazine may be an appropriate treatment option for patients with bipolar I depression and manic symptoms, with higher doses potentially more effective in patients with manic symptoms.

Keywords: Bipolar Depression, Mixed Manic Symptoms, Cariprazine, Bipolar I Disorder

Disclosure: Acadia, Alkermes, Allergan, Arbor Pharmaceuticals, AstraZeneca, Axovant, Biogen, Biopharma, Celgene, Forest, Forum, Genomind, Innovative Science Solutions, Intra-Cellular Therapies, Jazz, Lundbeck, Merck, Otsuka, PamLabs, Servier, Shire, Sunovion, Takeda, and Teva, Consultant, Genomind, Board Member, Forum, Lundbeck, Otsuka, Perrigo, Servier, Sunovion, and Takeda, Consultant, Acadia, Avanir, Braeburn Pharmaceuticals, Eli Lilly, Intra-Cellular Therapies, Ironshore, ISSWSH, Neurocrine, Otsuka, Shire, Sunovion, and TMS NeuroHealth Centers, Grant

W131. (R)-Ketamine, (S)-Ketamine and Their Metabolites Affect Differentially In Vivo Monoamine Release in the Prefrontal Cortex of Mice: Different Involvement of AMPA Receptors

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Background: Accumulating evidence indicates that the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine has rapid and potent antidepressant effects in major depressive disorder including treatment-resistant depression. Ketamine contains a chiral center producing two optical isomers (enantiomers), (R)-ketamine and (S)-ketamine. Several studies have demonstrated in animal studies that (R)-ketamine has a greater potency and longer-lasting antidepressant effects than (S)-ketamine. Additionally, some metabolites of ketamine such as (S)-norketamine ((S)-NK) and (2 R,6 R)-hydroxynorketamine ((2 R,6 R)-HNK) has been shown to exert antidepressant-like effects. However, the mechanistic details are not fully understood. The monoamine system in the prefrontal cortex has been implicated in the antidepressant actions of ketamine. Here we aimed to investigate the effects of (R)-ketamine, (S)-ketamine and their metabolites on the in vivo release of monoamines in the prefrontal cortex of mice.

Methods: All animal studies were approved by the Animal Care and Use Committee of the Graduate School of Pharmaceutical Sciences, Osaka University. All experimental procedures were conducted in accordance with the guidelines of the Guide for the Care and Use of Laboratory Animals. Eight-week-old male C57BL/6 J mice were used. In some experiments, lipopolysaccharide (LPS, 0.5 mg/kg)-induced depression-like model was used. Extracellular monoamine levels in the prefrontal cortex were measured by in vivo microdialysis.

Results: Both (R)-ketamine (10 and 20 mg/kg, intraperitoneally (i.p.)) and (S)-ketamine (10 and 20 mg/kg, i.p.) increased dose-dependently 5-HT release in normal mice, and the effect of (R)-ketamine was greater than that of (S)-ketamine. In contrast, (S)-ketamine caused a robust increase in dopamine release compared with (R)-ketamine. Both (R)-ketamine and (S)-ketamine increased noradrenaline release, but these effects did not differ significantly. (S)-NK (20 mg/kg, i.p.) increased dopamine and noradrenaline, but

not 5-HT, release. (2 R,6 R)-HNK (20 mg/kg, i.p.) increased 5-HT and noradrenaline, but not dopamine, release. In LPS-treated mice, (R)-ketamine and (S)-ketamine caused similar changes in prefrontal monoamine release as in normal mice, and there was a significant difference between the effects of ketamine enantiomers on 5-HT and dopamine release. An AMPA receptor antagonist NBQX inhibited (R)-ketamine-induced dopamine release and (S)-ketamine-induced 5-HT and dopamine release, but it did not affect (R)-ketamine-induced 5-HT or noradrenaline release or (S)-ketamine-induced noradrenaline release.

Conclusions: These results suggest that (R)-ketamine, (S)-ketamine, (S)-NK and (2 R,6 R)-HNK affect differentially serotonergic and dopaminergic neurotransmission in the prefrontal cortex. (R)-ketamine caused a greater increase in 5-HT release than (S)-ketamine, but this effect was AMPA receptor-independent. Ketamine-induced dopamine, but not noradrenaline, release was AMPA receptor-dependent. Further studies will be needed to clarify how the neurochemical differences observed here would be involved in the pharmacological differences between (R)-ketamine, (S)-ketamine, and their metabolites.

Keywords: R-(-)-ketamine, Esketamine, Microdialysis, (S)-Norketamine, Hydroxynorketamine

Disclosure: Nothing to disclose.

W132. Does Plasma Membrane Monoamine Transporter Function Undermine Antidepressant Effectiveness?

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Background: The poor effectiveness of antidepressants is hypothesized to be attributable, in part, to high volume transporters with low selectivity (i.e., "uptake-2" mechanisms) that undermine antidepressant blockade of highly selective, low volume transporters (i.e., "uptake-1" transporters) such as the serotonin transporter. Compared to other uptake-2 transporters in brain, plasma membrane monoamine transporter (PMAT, Slc29a4) preferentially transports serotonin and dopamine, both heavily implicated in the pathophysiology of depression. Therefore, we hypothesized that reduced function of PMAT would enhance the ability of antidepressants to elicit antidepressant-like behaviors in a forced swim test, and to impair clearance of extracellular serotonin. Because a selective pharmacologic inhibitor of PMAT has yet to be identified, genetic knockout of PMAT is currently the best available method for investigating PMAT's functional role.

Methods: Using a mouse line recently developed in the lab of Dr. Joanne Wang, we compared male and female wildtype (+/+) controls against mice with reduced (+/-) or completely ablated (-/-) PMAT function to evaluate how PMAT deficiency affects behavioral responses to antidepressants in the forced swim test. Sub-effective doses of the serotonin transporter inhibitor fluvoxamine (8 mg/kg), or the dopamine/norepinephrine transporter inhibitor bupropion (1 mg/kg), were given 30 min prior to a forced swim test (n = 2-5; experiments are ongoing; will be analyzed with two-way ANOVAs and Dunnett's post-hocs within sex). Durations of immobility, swimming, and climbing behaviors were scored by observers blind to sex, genotype, and treatment. We have also begun measuring serotonin clearance in the nucleus accumbens of male +/+ and -/- mice using in vivo high-speed chronoamperometry in the presence or absence of fluvoxamine and/or bupropion.

Results: Preliminary findings indicate that male -/- mice may selectively exhibit antidepressant-like responses to bupropion and fluvoxamine through an increase in swimming behavior (n = 3-5, $p < 0.01$, one-way ANOVA). In contrast, female -/- mice appear to exhibit a depressive-like response specifically to bupropion (n = 2-3). These studies are continuing. Ongoing experiments are also evaluating fluvoxamine- and/or bupropion-elicited changes in serotonin clearance in male +/+ and -/- mice.

Conclusions: These initial results support our hypothesis and suggest an unexpected sex-specific contribution of PMAT function in the poor effectiveness of uptake-1 targeting antidepressant drugs. Though chronoamperometry experiments are still in early stages, these will afford insight into possible neurochemical differences that could explain these intriguing sex differences. Given our early behavioral findings, greater focus on drug discovery for PMAT-selective inhibitors could reveal compounds that are useful as antidepressant adjuvants. Future work will focus on identifying potential mechanisms through which these sex- and genotype-dependent antidepressant responses are mediated.

Keywords: Plasma Membrane Monoamine Transporter, Antidepressant Response, Monoamines, Sex Differences

Disclosure: Nothing to disclose.

W133. Lack of Deuterium Isotope Effects in the Antidepressant Effects of (R)-Ketamine in a Chronic Social Defeat Stress Model

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Background: The N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine is one of the most attractive antidepressants since this drug can produce rapid-onset and sustained antidepressant effects in treatment-resistant patients with major depression and bipolar disorder. (R,S)-Ketamine (Ki = 500 nM for NMDAR) is a racemic mixture containing equal parts of (S)-ketamine (esketamine: Ki = 300 nM) and (R)-ketamine (Ki = 1,400 nM). (R)-Ketamine showed greater potency and longer lasting antidepressant effects than (S)-ketamine in the animal models of depression (Zhang et al, 2014; Yang et al, 2015; Fukumoto et al, 2017). Unlike (S)-ketamine, (R)-ketamine does not induce psychotomimetic-like behavioral side effects in rodents (Yang et al, 2015; 2016; Hashimoto et al., 2017). Taken together, it is likely that (R)-ketamine could be a safer antidepressant without psychotomimetic side effects in humans than (S)-ketamine (Hashimoto, 2016). (R)-ketamine is known to be metabolized to (R)-norketamine by P450 enzyme in the liver, subsequently to (2 R,6 R)-hydroxynorketamine (HNK). Zanos et al. (2016) reported that metabolism of (R,S)-ketamine to (2 R,6 R)-HNK(Ki > 10,000 nM for NMDAR) was essential for (R,S)-ketamine-mediated antidepressant activity. They reported the deuterium isotope effects at the C6 position in the metabolism and antidepressant actions of (R,S)-ketamine (Zanos et al, 2016). The purpose of the present study is to compare the metabolism and antidepressant effects of (R)-ketamine, and (R)-d2-ketamine in a chronic social defeat stress (CSDS) model.

Methods: Eight-week-old adult male C57BL/6 mice (weight, 20–25 g; Japan SLC, Inc., Hamamatsu, Japan) were used. To determine the plasma and brain concentration–time profiles, blood and brain samples were collected 10, 30, 60, 120, and 240 min after intraperitoneal (i.p.) administration of (R)-ketamine

(10 mg/kg) or (R)-d2-ketamine (10 mg/kg). To simultaneously determine (R)-ketamine, (R)-norketamine, and (2 R,6 R)-HNK levels in the plasma and brain, 5 μL of the resulting supernatant was subjected to an enantioselective liquid chromatography–tandem mass spectrometry (LC–MS/MS) assay with some modifications to the procedure (Chang et al, 2018; Yamaguchi et al, 2018). Saline (10 ml/kg), (R)-ketamine (10 mg/kg), or (R)-d2-ketamine (10 mg/kg) was administered i.p. into CSDS susceptible mice. Furthermore, saline (10 ml/kg) was administered i.p. into control (no CSDS) mice. Behavioral tests including locomotion, tail suspension test (TST), forced swimming test (FST) and 1% sucrose preference test (SPT) were performed.

Results: Pharmacokinetic studies showed that levels of (2 R,6 R)-d1-HNK, a final metabolite of (R)-d2-ketamine, in the plasma and brain after administration of (R)-d2-ketamine (10 mg/kg) were significantly lower than those of (R)-ketamine (10 mg/kg), indicating deuterium isotope effects in the production of (2 R,6 R)-HNK. In contrast, levels of (R)-ketamine and its metabolite (R)-norketamine in the plasma and brain were the same for both compounds. In a CSDS model, both (R)-ketamine (10 mg/kg) and (R)-d2-ketamine (10 mg/kg) showed rapid and long-lasting (7 days) antidepressant effects, suggesting no deuterium isotope effects in the antidepressant effects of (R)-ketamine.

Conclusions: The present study suggests that deuterium substitution of hydrogen at the C6 position significantly slowed the metabolism from (R)-ketamine to (2 R,6 R)-HNK in mice. Furthermore, we did not find the deuterium isotope effects in terms of the rapid and long-lasting antidepressant effects of (R)-ketamine in a CSDS model. Therefore, it is unlikely that (2 R,6 R)-HNK is essential for antidepressant effects of (R)-ketamine.

Keywords: R-(-)-ketamine, Hydroxynorketamine, Racemic Ketamine and Metabolites, Ketamine, Fast-acting Antidepressant

Disclosure: Inventor of the patent on R-ketamine, Patent, Inventor of the patent on S-norketamine, Patent

W134. Sequential Treatment With IV Ketamine Followed by Combined Oral D-Cycloserine + Lurasidone (NRX-101) for Severe Bipolar Depression and Suicidality: Preclinical and Clinical Findings

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Background: N-methyl-D-aspartate (NMDAR) antagonists produce potent anti-depressive and anti-suicidal effects in humans but their clinical utility is limited by psychotomimetic side effects and lack of orally available medications. D-cycloserine (DCS) is a NMDAR/glycine-site mixed agonist/antagonist that has shown efficacy at high doses (1000 mg) in human clinical studies in treatment-resistant depression (TRD) and suicidality. Lurasidone is an atypical antipsychotic approved for the treatment of bipolar depression. Here, we evaluated effects of combined DCS + lurasidone (NRX-101) in rodent depression, psychosis, and anxiety/akathisia assays. In parallel, we evaluated the ability of oral NRX-101 to maintain effects of acute ketamine administration in patients with severe bipolar depression with acute suicidal ideation and behavior (ASIB).

Methods: In preclinical studies, the combination of DCS and lurasidone was assessed in animal models of depression (Forced swim test, FST), psychosis (AMPH-induced locomotor activity, LMA), anxiety/akathisia (Elevated plus maze, EPM) and abuse potential (ketamine self-administration) relative to plasma levels associated with clinical response.

In the clinical study, patients with severe bipolar depression that were acutely suicidal of either sex ($n = 21$) were first administered intravenous ketamine vs. placebo. Responders were then randomized to receive co-formulated DCS + lurasidone (NRX-101) vs. lurasidone alone. Safety and tolerability were assessed along with achieved plasma level.

Results: DCS significantly reduced immobility in the FST in a dose-dependent fashion across doses of 30 – 1000 mg following either oral ($p < .0001$) or ip ($p < .0001$), consistent with high dose antagonist effects. In contrast, lurasidone (0.2 -3.0 mg/kg) alone significantly increased immobility in the FST despite clinical antidepressant effects ($p = .036$). Immobility-reducing effects of high-dose DCS persisted in the presence of lurasidone administered at doses of 0.2 ($p < .0001$), 1.0 mg/kg ($p < .0001$) or 3.0 mg/kg ($p < .0001$). Moreover, high-dose DCS blocked the lurasidone-induced increase in FST ($p = .5$).

In the LMA assay, DCS significantly increased AMPH-induced activity ($p = .041$), while lurasidone decreased activity ($p < .0001$). The combination of DCS + lurasidone produced activity levels that were not significantly different from those observed under control conditions ($p = .73$).

In the EPM assay, treatment with lurasidone (0.2 mg/kg) alone significantly reduced % time spent in the open arm in the absence of DCS ($p = .008$), indicated increased anxiety/akathisia. By contrast, DCS significantly increased % time in the open arm across the absence and presence of lurasidone ($p < .001$) and prevented lurasidone effects as shown by a non-significant lurasidone effect in the presence of DCS ($p = .2$). The lurasidone X DCS interaction ($p = .006$) was statistically reliable, indicating significant modulation of the lurasidone effect by DCS.

In the self-administration assay, ketamine induced escalating self-reinforcing behavior over time ($p < .0001$). S-Ketamine significantly substituted for ketamine. By contrast, DCS showed no substitution effect, suggesting absence of abuse liability.

In the clinical study, patients overall showed acute reduction in depression and suicidality. Achieved plasma levels were consistent with a priori expectations. Overall, the medication was well tolerated. No medication-related serious or unexpected adverse events were observed.

Conclusions: Though highly overlapping with depression, suicidality is emerging as an independent biological target. Although NMDAR antagonists such as ketamine have shown reproducible reductions in both depression symptoms and suicidality, usage is severely limited by lack of orally available formulations and high abuse potential of specific agents, such as ketamine. DCS is a clinically available anti-tuberculosis agent (Seromycin®) that has been marketed for over 50 years with a well-documented safety profile and low abuse potential. Antidepressive effects were first noted over 50 years ago and have been replicated over recent years. In addition, effects have been observed not only on treatment resistant symptoms of depression, but also on associated suicidal symptoms.

Here, we evaluate the preclinical pharmacological profile of DCS in combination with lurasidone, a drug approved for treatment of depressive symptoms in bipolar disorder. DCS produced significant anti-depressant effects at doses associated with plasma levels in excess of 25 μg/mL, consistent with its NMDAR mixed agonist/antagonist properties. In addition, DCS significantly reversed lurasidone-associated anxiety/akathisia while lurasidone reversed DCS-induced increases in locomotor hyperactivity, reflecting unique synergistic effects of the combination.

In an initial clinical study, co-formulated DCS + lurasidone (NRX-101) was found to be safe and well tolerated, and to produce plasma DCS levels in the therapeutic range. Overall, these findings support continued clinical development for NRX-101 for maintenance of ketamine effects in the treatment of bipolar depression associated with acute suicidal ideation and behavior (ASIB).

Keywords: Bipolar I Depression, NMDA Receptor, Suicidality, d-Cycloserine, Lurasidone

Disclosure: NeuroRx, Board Member, NeuroRx, Stock / Equity, NeuroRx, Patent, Glytech, Patent, Glytech, Stock / Equity, AASI, Patent, Promentis, Advisory Board, Phytecs, Advisory Board, Lundbeck, Consultant, Concert, Consultant, Autifony, Consultant, Forum, Consultant, Takeda, Consultant

W135. Role of GluN2B Receptor in the Long-Lasting Antidepressant Effects of (2 R,6 R)-Hydroxynorketamine

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Background: Recently, (2 R,6 R)-hydroxynorketamine ((2 R,6 R)-HNK), a metabolite of ketamine, has been reported to produce rapid and long-lasting antidepressant effects in rodents without the ketamine-related side effects. We have also found that (2 R,6 R)-HNK induces long-lasting antidepressant actions via activity-dependent stimulation of VDCC, BDNF release, and mTORC1 signaling in mPFC. Previous studies show that the actions of ketamine require similar signaling mechanisms, and this is thought to occur via induction of glutamate neurotransmission by the blockade of NMDA receptors on GABA interneurons. In addition, previous studies point to the blockade of GluN2B -containing NMDARs as the critical mediator for the rapid antidepressant effects of ketamine. Recent studies demonstrate that (2 R,6 R)-HNK also causes a transient burst of glutamate. Initial studies reported that (2 R,6 R)-HNK does not act via NMDA receptors, although there are conflicting reports, and the initial cellular target of (2 R,6 R)-HNK remains unclear. To investigate this important question, we have examined the involvement of the GluN2B receptor in the actions of (2 R,6 R)-HNK using a cell specific knockdown approach.

Methods: To examine the involvement of the GluN2B receptor on pyramidal neurons vs. GABA interneurons in the antidepressant effects of (2 R,6 R)-HNK, we used cell specific Cre recombinase transgenic mice, including calicium/calmodulin -dependent protein kinase type 2CRE (Camk2)CRE, glutamic acid decarboxylaseCRE (Gad)CRE), parvalbumincre (Pv)CRE, somatostatinCRE (Sst) CRE mice) and wild-type mice (C57BL/6 J) were bilaterally infused with adeno-associated virus-2 (AAV2) NR2BshRNA into mPFC. After over 3 weeks of recovery, forced swimming test (FST), novelty suppressed feeding test (NSFT), and locomotor activity test were carried out, and the expression of NR2B receptors in the mPFC were examined.

Results: (2 R,6 R)-HNK exerted long-lasting antidepressant effects in FST and NSF, without affecting locomotor activity in wild-type mice. The actions of (2 R,6 R)-HNK were blocked in AAV2NR2BshRNA-treated GADCRE mice but not CAMK2CRE mice. In addition, Infusions of AAV2NR2BshRNA blocked the actions of (2 R,6 R)-HNK in PVCRE and SSTCRE mice. The NR2B expressions in the mPFC were reduced in AAV2NR2BshRNA-treated CAMK2CRE, GADCRE, PVCRE and SSTCRE mice.

Conclusions: These results suggest that the blockade of NR2B receptors on GABA interneurons, expressing PV and SST, but not pyramidal neurons plays an essential role in the actions of (2 R,6 R)-HNK, indicating that (2 R,6 R)-HNK blocks the NR2B receptors on GABA interneurons and induces glutamate neurotransmission, and subsequent long-lasting antidepressant effects. Our results also indicate that AAV2NR2BshRNA reduced the expressions of NR2B receptors in the mPFC in Cre-dependent manner in CAMK2CRE, GADCRE, PVCRE and SSTCRE mice. Further studies are being conducted to examine the effects of (2 R,6 R)-HNK on NMDA receptors on pyramidal neurons and GABA interneurons.

Keywords: Hydroxynorketamine, Ketamine, Depression, NR2B Receptor, GABA

Disclosure: Nothing to disclose.

W136. Buprenorphine in Combination With Samidorphan Reverses Kappa Agonist-Induced Deficit on Immobility Behavior in Wistar Kyoto Rats

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Background: The endogenous opioid system is thought to play a key role in the regulation of mood [1Lutz and Kieffer 2013; Trends Neurosci, 2013. 36(3): p. 195-206]. ALKS 5461(BUP/SAM) is an opioid system modulator in development as an adjunctive treatment for major depressive disorder that combines buprenorphine (BUP) with samidorphan (SAM). We have previously described that combining BUP and SAM produced an antidepressant-like behavioral effect in rats in the forced swim test (FST) and that these effects were dependent on mu opioid receptor (MOR) activity [Smith et al., 2017; Neuropsychopharmacology, 2017. 42: p. S476]. However, the relative contribution of kappa opioid receptors (KOR) to this behavioral effect is unclear. Activation of KOR produces aversive states in both rodents and humans [Knoll et al., 2010; Brain Res, 2010. 1314: p. 56-73]. In fact, a selective KOR antagonism has been suggested as a druggable mechanism for the treatment of MDD. Here, we have characterized the role of KOR on immobility behavior in Wistar Kyoto (WKY) rats subjected to the FST using a pharmacological approach with selective agonist U50,488 and antagonist nor-BNI. We demonstrate that BUP/SAM reverses a KOR agonist-induced deficit in the FST.

Methods: Male WKY rats (Charles River, Kingston, NY) were employed ($n = 8$/group) for these studies as they spontaneously exhibit high levels of immobility in the FST [4]. To selectively block KOR activity, nor-BNI (0, 1, 3 or 10 mg/kg SC) was administered 24 h before being placed into the FST apparatus (water temparature 23 ± 1°C, and water depth 32 cm) for a single 5 min test session. To investigate the effect of KOR agonism, rats were administered with U50,488 (0, 0.5, 1 or 5 mg/kg SC) and tested in the FST. Based on previously published BUP/SAM behavioral responses, immobility behavior was measured 3 h and 24 h post-drug treatment. Finally, to further explore the mechanism of the BUP/SAM response in the WKY FST, we co-administered U50,488 (0 or 0.5 mg/kg SC) with BUP (0.1 mg/kg)/SAM (0.3 mg/kg) and tested in the FST 3 h later. All behavior was video-recorded and scored manually by an experienced analyst. Data are expressed as mean + SEM and were analyzed as an ANOVA, with follow-up post hoc analysis or t-test where appropriate.

Results: The KOR antagonist nor-BNI had no effect on immobility in WKY rats ($F(3,21) = 1.622$; $p > 0.05$). The selective KOR agonist U50,488 had no overall effect on immobility behavior in WKY rats at 3 h ($F(3,21) = 1.704$; $p > 0.05$) or 24 h ($F(3,21) = 0.096$; $p > 0.05$). However, there was an inversed dose response curve observed at 3 h and the lowest dose of U50,488 significantly increased immobility compared to vehicle-treated rats ($p < 0.01$; unpaired t test). In a separate cohort of rats, BUP (0.1 mg/kg)/SAM (0.3 mg/kg) significantly reduced immobility compared to vehicle treated controls 3 h post-drug administration. U50,488 (0.5 mg/kg) significantly increased immobility and this effect was completely blocked by co-administered BUP/SAM (0.1/0.3 mg/kg). In WKY rats,

KOR mRNA expression was higher in the amygdala vs. SD rats, no difference in MOR expression was observed in the amygdala.

Conclusions: Here we show that KOR antagonism alone did not significantly alter behavioral responses in the FST in WKY rats suggesting that KOR's are not necessarily critical for this behavioral response in this rat strain. However, we also report that immobility responses to KOR ligands differ significantly from previous published studies using other rat strains. These data may suggest that the KOR expression/function in the WKY rat is dysregulated. U50,488-induced immobility was completely blocked by BUP/SAM indicating that the combination may exert its pharmacological effect via functional antagonism of the KOR under conditions where KOR activity is enhanced in the rat e.g. chronic stress, aversion. Our previously presented work demonstrated that MOR's play a critical role mediating adaptive responses to immobility in the FST [2]. In these studies, modulation of MOR activity with a combination of BUP and SAM produced rapid and sustained reduction of immobility behaviors in WKY rats, an effect blocked by selective MOR antagonism. Taken together, these results may indicate that modulation of both MOR and KOR activity may be involved in the anti-immobility effect of the BUP/SAM combination in the FST.

Keywords: Buprenorphine, Samidorphan, Kappa Opioid Receptor

Disclosure: Karen Smith, Employee

W137. 5-HT1A Receptor Stimulation in the Medial Prefrontal Cortex Mediates the Antidepressant Effects of mGlu2/3 Receptor Antagonist and Ketamine

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Background: Metabotropic glutamate 2/3 (mGlu2/3) receptor antagonists have been demonstrated to show ketamine-like antidepressant profiles in rodents; rapid-acting and long-lasting antidepressant effects and efficacy in treatment-resistant depression models. We previously reported that serotonergic transmission plays a critical role in the antidepressant effects of both mGlu2/3 receptor antagonists and ketamine. Both mGlu2/3 receptor antagonist and ketamine reportedly increased serotonin (5-HT) release in the medial prefrontal cortex (mPFC) through AMPA receptor stimulation, and the antidepressant effects of both compounds were abolished by depletion of 5-HT and a 5-HT1A receptor antagonist. However, the detailed mechanisms of involvement of serotonergic system in the actions of both compounds still remain to be fully explored. Among the 5-HT receptor subtypes, the 5-HT1A receptor in the mPFC has an important role in depression and antidepressant actions. Here, we investigated the role of the mPFC 5-HT1A receptor and its downstream signaling mechanisms in the antidepressant effects of LY341495, an mGlu2/3 receptor antagonist, and ketamine.

Methods: The sustained antidepressant effects were evaluated in the mouse forced swimming test (FST) at 24 h after intraperitoneal administration of LY341495 or ketamine. 8-OH-DPAT, a 5-HT1A receptor agonist, was administered either subcutaneously or intra-mPFC at 24 h prior to the FST. The roles of 5-HT1A receptor and its signaling mechanisms (phosphoinositide-3-kinase (PI3K)/Akt) in the mPFC were investigated by intra-mPFC injection of WAY100635 (a 5-HT1A receptor antagonist) or LY294002 (a PI3K inhibitor). Akt phosphorylation in the mPFC was determined by western blotting. Because PI3K/Akt signaling activates mechanistic target of rapamycin complex 1 (mTORC1) signaling, role of mTORC1 signaling was investigated by intra-mPFC injection of rapamycin (an mTORC1 inhibitor).

Results: Both LY341495 and ketamine significantly reduced immobility time in the FST, which lasted for 24 h after a single administration (sustained antidepressant effects), and the sustained antidepressant effects of both compounds were attenuated by intra-mPFC injection of WAY100635. The sustained antidepressant effects were mimicked by intra-mPFC, but not subcutaneous, administration of a 5-HT1A receptor agonist, 8-OH-DPAT, indicating that selective stimulation of the mPFC 5-HT1A receptor is necessary to exert the sustained antidepressant actions. The sustained antidepressant effects of LY341495, ketamine and 8-OH-DPAT were abrogated by intra-mPFC injection of LY294002. LY341495 and ketamine increased the phosphorylation of Akt in the mPFC, which was blocked by intra-mPFC injection of either WAY100635 or LY294002. Therefore, activation of PI3K/Akt signaling in the mPFC, presumably via stimulation of 5-HT1A receptor, has an important role in the sustained antidepressant effects of LY341495 and ketamine. Furthermore, the sustained antidepressant effects of LY341495, ketamine and 8-OH-DPAT were attenuated by intra-mPFC injection of rapamycin.

Conclusions: These results indicate that selective stimulation of the mPFC 5-HT1A receptor and subsequent activation of the PI3K/Akt/mTORC1 pathway are necessary for LY341495 and ketamine to exert the sustained antidepressant effects. Because the mGlu2/3 receptor antagonist shares synaptic and neural mechanisms with ketamine to exert the sustained antidepressant effects, the present findings underpin the proposal that mGlu2/3 receptor antagonists can be an alternative to ketamine.

Keywords: mGlu2/3 antagonist, Ketamine, 5-HT1A receptors, Antidepressant

Disclosure: Taisho Pharmaceutical Company Ltd., Employee

W138. Peripheral Inflammation is Associated with Worse Acute-Phase Antidepressant Outcomes in Females but Not in Males: Findings From the EMBARC Study

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Background: Peripheral inflammation is associated with poor response to antidepressant treatments in patients with major depressive disorder. Whether this association differs on the basis of gender remains unknown.

Methods: Participants included those who were enrolled in the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study, were randomized to either sertraline or placebo, and had baseline plasma samples available ($n = 220$; male $n = 75$, female $n = 145$). Severity of depressive symptoms was measured with the 17-item Hamilton Rating Scale for Depression (HAMD-17) at baseline and weeks 1, 2, 3, 4, 6, and 8. C-reactive protein (CRP), a biomarker of peripheral inflammation, was measured in plasma samples with commercially-available ELISA kits at baseline, week-1 and week-8. A mixed model analysis with gender-by-baseline logCRP-by-time interaction was used to test for gender-specific differences in HAMD-17 change from baseline to week-8 as predicted by baseline logCRP levels. Additional analyses tested for any differences in males and females in logCRP change from baseline to week-8 as well as any gender-specific differences in association of baseline to week-8 changes in logCRP and HAMD-17. Post-hoc analyses stratified by gender were used to interpret statistically significant gender interactions. All analyses included

body mass index, site, smoking status, and age were included as covariates.

Results: There was a statistically significant gender-by-baseline logCRP-by-time interaction ($F = 2.44$, $df = 5$, 797, $p = 0.033$) in mixed model analyses with HAMD-17 as the dependent variable. In subsequent analyses stratified by gender, higher baseline CRP was associated with lower baseline to week-8 HAMD-17 reduction in females ($p < 0.0001$) but not in males ($p = 0.632$). While logCRP decreased significantly from baseline to week-8 ($p = 0.041$), there were no gender differences ($p = 0.249$). There was no significant gender-specific association between baseline to week-8 changes in HAMD-17 and logCRP ($p = 0.238$).

Conclusions: In a large study of depressed outpatients, we replicated previous findings that elevated baseline CRP is associated with worse antidepressant treatment outcomes. However, this effect was limited only to females. There were no gender-specific differences either in CRP changes with treatment or in association of changes in CRP and depression severity with acute-phase antidepressant treatment.

Keywords: CRP, Sex Differences, Depression, Antidepressant Response, inflammation

Disclosure: Acadia Pharmaceuticals, Grant, Janssen Research, Grant

W139. Living at Moderate Altitude May Alter Brain Monoamines to Worsen Mood and Substance Use Disorders: A Sex-Based Animal Model Study

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Background: Demographic studies show that living at altitude is a risk factor for depression, suicidal behavior, and abuse of methamphetamine and cocaine, implying that hypobaric hypoxia may alter brain physiology to detrimentally impact human behavior. In an animal model, we find that depression-like behavior (DLB), anxiety and methamphetamine-paired conditioned place preference all increase with altitude of housing in female rats (4,500 ft or 10,000 ft vs. sea level), but not males. However, both male and female rats housed at altitude fail to respond to most SSRIs, implying that an altitude-related change in brain physiology occurs in a sex-based manner. In the current study, we therefore examined the impact of a week of housing at moderate altitude on brain monoamines -the major neurotransmitters implicated in mood and substance abuse- in brain regions involved in mood and reward systems.

Methods: Male and female Sprague Dawley rats were housed for a week at 4,500 ft (4.5 K, local conditions) or 10,000 ft (10 K), vs. another group assayed after acclimatization at local conditions (baseline or D0). Rats were sacrificed, and brain regions dissected out. The prefrontal cortex (PFC), striatum (STR), hippocampus (HIPP) and brainstem (BST) were analyzed by ELISA for serotonin (5HT), dopamine (DA) or norepinephrine (NE).

Results: 1. Serotonin: (a) FEMALES: Housing at altitude decreased 5HT significantly in the female PFC ($F(2,24) = 15$, $p < 0.0001$) and STR ($F(2,25) = 6$, $p = 0.005$), with a 30% decrease in the PFC and a 50% decrease in the STR the 4.5 K or 10 K groups vs. D0 ($p < 0.05$). In the HIPP, a trend towards significance was seen ($F(2,26) = 3.1$, $p = 0.06$) but not in the BST ($F(2,26) = 1.1$, $p > 0.05$). (b) MALES: In the male PFC, altitude reduced 5HT more moderately ($F(2,27) = 5$, $p = 0.01$). A trend for reduced 5HT was seen in the STR ($F(2,24) = 3$, $p = 0.07$), but no change was seen in the male HIPP ($F(2,26) = 0.8$, $p > 0.05$). Altitude altered 5HT in the male BST ($F(2,27) = 4.7$, $p = 0.02$), with 5HT increased by 60% in the 4.5 K group vs. D0 ($p < 0.05$).

2. Dopamine: (a) FEMALES: In females, DA increased with housing at altitude, in the PFC ($F(2,29) = 9.6$, $p = 0.0006$), STR ($F(2,30) = 21$, $p < 0.0001$) and the BST ($F(2,33) = 11$, $p = 0.0002$), but not in the HIPP ($F(2,33) = 2.0$, $p > 0.05$). In post hoc tests, the 10 K group was significantly higher vs. D0 and 4.5 K groups in the female PFC (150% increase from baseline, $p < 0.005$) and BST (70% increase, $p < 0.05$). In the STR, the 10 K and 4.5 K groups were significantly higher vs. D0 (300%, 400% increase, $p < 0.0005$). (b) MALES: In stark contrast to females, males showed an altitude-related decrease in DA in the PFC ($F(2,21) = 6$, $p = 0.008$), STR ($F(2,31) = 12$, $p = 0.0002$), HIPP ($F(2,32) = 6$, $p = 0.005$) and BST ($F(2,29) = 11$, $p = 0.0003$). A 70-80% decrease in DA was seen for 10 K vs D0 in the PFC ($p < 0.01$), the STR ($p < 0.005$), HIPP ($p < 0.05$) and the BST ($p < 0.05$), while the 4.5 K group was 50% lower vs. D0 in the PFC and 40% lower in DA in the BST.

3. Norepinephrine: (a) FEMALES: For NE, an altitude-related trend was seen towards significance in the PFC ($F(2,25) = 2.9$, $p = 0.07$), a significant change in NE was seen in the female STR ($F(2,25) = 9$, $p = 0.001$) and HIPP ($F(2,26) = 3.8$, $p = 0.03$), but not in the BST ($F(2,20) = 1.3$, $p > 0.05$). Females at 4.5 K showed a 125% increase in NE in the STR and a 50% in the HIPP ($p < 0.01$). (b) MALES: Altitude did not alter NE in the male PFC ($F(2,30) = 1.07$, $p > 0.05$) or STR ($F(2,29) = 2.7$, $p > 0.05$). NE levels changed with altitude in the male HIPP ($F(2,24) = 7.3$, $p = 0.003$) and BST ($F(2,29) = 11.7$, $p = 0.0002$), with a 30% decrease at 10 K vs. D0 ($p < 0.05$).

Conclusions: To our knowledge, this is the first sex-based study on the effect of hypobaric hypoxia on brain monoamines at moderate altitudes, which may serve as representative of what people residing in the Rocky Mountain States experience. Previous studies on the impact of altitude/hypoxia on brain monoamines have been restricted to high altitude exposures > 18,000 ft, with respect to mountaineering, and have solely been conducted using males. (1) Serotonin: Housing at moderate altitude (4.5 K, 10 K) for a week significantly decreased 5HT levels in female PFC (by 30%) and STR (by 50%), suggesting a causal connection to greater DLB and anxiety in female rats at altitude in our model. While males show a small decrease in 5HT in the PFC and STR (30% at 10 K only), they also show the potential for recovery: serotonin levels increased by 60% in the BST (the site of serotonergic neurons), after a 2nd week at 4,500 ft. This may explain why males do not show an altitude-related increase in DLB or anxiety in this model. This altitude-related loss in brain 5HT accounts for the loss of function of the SSRIs Prozac®, Paxil® and Lexapro® in both sexes in our model. (2) Dopamine: DA significantly increases in the female PFC (by 150% at 4.5 K) and the STR (by 300% at 4.5 K or 400% at 10 K) but decreases with altitude in male rats in this model (50-80% decrease in PFC, STR). This sexual dimorphism in dopamine levels could explain why females show an altitude-related increase in conditioned place preference for methamphetamine, while males do not. (3) Norepinephrine: Females show an increase in NE at 4.5 K in the STR and HIPP, while males showed a decrease in NE at 10 K in the HIPP and BST. The sex-based dimorphism observed here may reflect sex-based differences in response to stress noted previously and could contribute to altitude-related deficits in mood, anxiety, cognitive function and risk for substance abuse previously noted. (Study funded by USTAR, MIRECC & VA Merit Review to PR.)

Keywords: Animal Models, Serotonin, Dopamine, Mood and Anxiety Disorders, Substance Abuse Disorders

Disclosure: Nothing to disclose.

W140. Chronic Treatment With Bifidobacterium (Longum, Breve, Infantis) Modulates GABAA Receptor Gene Expression, Neuronal Function and Structure in the Rat Hippocampus

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Background: Changes in microbiota alter the modulation of the hypothalamic-pituitary-adrenal (HPA) axis sensitivity, to the effect of stress, an effect that may involve the inhibitory neurotransmitter GABA, one of the neurotransmitters known to modulate of emotional states. In our laboratory we studied in adult rats the effect of long-lasting effect of a 1-2 months chronic treatment with a preparation of three different Bifidobacterium (Longum, Breve, Infantis) on GABAA receptor gene expression and GABAergic function and structure in the hippocampus as well as the HPA axis sensitivity to acute foot-shock stress.

Methods: Were used adult male rats of Sprague Dawley strain. Rats were treated for 1 or 2 month per os, once a day, with a mixture of different three different Bifidobacterium: longum (BB536 strain, final concentration of 3*109 CFU), brevis (M-16 strain, final concentration of 1*109 CFU) and infantis (M-63 strain, final concentration of 1*109 CFU). In these rats were carried out the following studies in hippocampus: Western blot to assess the changes in α1, α4, δ and γ 2, GABAA receptor subunit and BDNF protein expression. We used a specific antibody against α1, α4, δ and γ2 (1:250; Phosphosolution) and BDNF (1:500; Santa Cruz Biotecnology). A specific antibody against GAPDH (1:1000; Millipore, USA) was used as standard; immunoistochemistry to assess the changes in α1, α4, δ and γ 2 GABAA receptor subunit in specific subareas of hippocampus. We used the same antibodies used for western blot experiments; electrophysiology, to assess the GABAergic tonic current and spontaneous GABAA receptor–mediated ISPCs (sIPSCs) current; Golgi impregnation, to assess the dendritic spines density; ELISA to assess the amount of corticosterone on plasma and allopregnanolone in the brain

Results: Plasma corticosterone (CTS) levels were measured in basal condition and after foot-shock stress in animals previously treated with bifidobacterium. This treatment failed to change the basal content as well as the increase of CTS levels elicited by acute footshock stress when compared to vehicle treated group. In contrast, western blot and immunohistochemistry analysis showed that two months of bifidobacterium treatment reduced α1, α4, and δ GABAAR subunits expression while increasing γ2 subunit. Moreover, this treatment significantly reduced plasma content of allopregnanolone, an agonist ligand for GABAA receptor containing α4 and δ subunits. Patch-clamp experiments performed in dentate gyrus granule cells showed no changes in synaptic currents while the tonic component of GABAergic inhibition was significantly decreased. The latter data are consistent with an observed increase of neuronal excitability measured in the same neurons of the dentate gyrus as well as with the parallel reduction of δ subunit and AP plasma content. Moreover, more recently we found that the same chronic treatment with bifidobacterium increased the number of dendritic spines in CA1 pyramidal neurons and in the granule cells of dentate gyrus.

Conclusions: Altogether our data show that this mixture of three (Longum, Brevis and Infantis) bifidobacterium given chronically to rats is able to modify the gene expression of specific GABAA receptor subunits in the rat hippocampus, an affect associate to functional and morphological changes of specific neuronal populations of dentate gyrus and CA1 and further support the crucial role of specific gut bacteria in the modulation of accordingly brain function. Accordingly, the concept of psychobiotics as new tools to be used in mental health has been recently suggested

Keywords: GABA-A Receptors, Dendritic Spines, Electrophysiology

Disclosure: Nothing to disclose.

W141. Induction and Quantification of Plasticity in Human Cortical Networks

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Background: How does repetitive stimulation induce cortical plasticity in the human brain? Knowledge of the neural mechanism underlying how brain stimulation modulates neural activity is necessary to develop next-generation personalized brain stimulation treatments for depression and other neuropsychiatric disorders. Previous work in our lab demonstrated that repetitive stimulation elicited effects that outlasted the stimulation period and could be predicted based on pre-stimulation network characteristics. However, the dynamics underlying plasticity induction and the relationship to longer-term effects remains unknown.

Methods: Here, we applied direct electrical stimulation in 14 patients with medically-intractable epilepsy and examined neural dynamics during the stimulation session. We applied 10 Hz trains of electrical pulses at a 5 s on, 10 s off pattern (3000 pulses total) in order to mimic patterns used for non-invasive brain stimulation. Patients were cognizant that the experiment was occurring but could not differentiate when they were receiving stimulation. Neural changes were assessed using high gamma (70-120 Hz) power, thought to be a correlate of population neuronal activity. Cortical dynamics during the stimulation period were assessed by examining (1) intra-train and (2) inter-train effects. Longer-lasting neural changes were assessed using pre- and post-stimulation single pulse cortico-cortical evoked potentials and resting HGP connectivity.

Results: 10 Hz induced significant changes in neural activity on multiple timescales. High gamma power (HGP) increased during the train (intra-train) and decreased following the train (inter-train), for up to 8 s after the train ended. Intra-train HGP changes predicted subsequent inter-train HGP changes. In a subset of patients, repetitive trains elicited sequentially stronger intra-train HGP increases and inter-train HGP decreases, which related to long-term changes following the stimulation session. Both intra-train and inter-train effects predicted effects that outlasted the stimulation session, and together with pre-stimulation network characteristics, correctly predicted the location, strength, and polarity of post-stimulation effects.

Conclusions: We conclude that cortical dynamics can be monitored during the 10 Hz stimulation session, yielding both a detailed mechanistic look at brain plasticity and the potential for real-time applications. Together, this work demonstrates that repetitive stimulation induces a buildup of neural changes that reflect an overall increase in excitability in the stimulation network. Future work includes designing optimized closed-loop technologies and translation to non-invasive methodology.

Keywords: TMS, Epilepsy, Neuroplasticity, EEG

Disclosure: Nothing to disclose.

W142. NYX-2925 Facilitates NMDAR-Dependent NREM Sleep and Learning and Memory in Rats: A Translational Approach for Measuring NMDAR-Dependent Synaptic Plasticity

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Background: NYX-2925 is a novel, oral, small-molecule NMDA receptor (NMDAR) modulator originating from a spiro-beta-lactam based chemical platform and is distinct from known NMDA receptor agonists or antagonists. NYX-2925 is in development as a therapy for chronic pain and is currently under evaluation in two Phase 2 clinical studies, one in subjects with painful diabetic peripheral neuropathy and the other in subjects with fibromyalgia (ClinicalTrials.gov identifiers: NCT03219320; NCT03249103). Both indications being studied are chronic pain conditions in which sleep disruption is often a core symptom reported by those affected. NYX-2925 facilitates synaptic plasticity as measured by enhancement of long-term potentiation (LTP) both in vitro and ex vivo 1-7 days post-dosing (1-10 mg/kg, PO) in rats. NYX-2925 also enhances NMDAR-dependent positive emotional learning and novel object recognition memory (1 mg/kg, PO) in rats.

In this study, NMDAR-dependent non-REM (NREM) sleep as well as NMDAR-dependent learning and memory were used as in vivo measures of the enhancement of NMDAR activity by NYX-2925.

Methods: Sleep was recorded from skull surface electroencephalogram (EEG) electrodes and neck muscle electromyography (EMG) electrodes in 2-3-month-old male Sprague-Dawley rats. A 6-hour sleep-deprivation protocol was used (Pinnacle Technology, USA) and either NYX-2925 (0.1, 1, 10 mg/kg PO) or vehicle was dosed 1-hour before testing. Sleep was measured during the 12-hour sleep cycle (lights on). NMDAR-dependent learning and memory was also assessed using the positive emotional learning test in sleep-deprived rats.

Results: NYX-2925 increased total sleep time and NREM sleep time without affecting REM sleep time. Delta power was increased during NREM. Whereas delta power was decreased during wake. Sleep deprivation suppressed NMDAR-dependent positive emotional learning, and this effect was rescued by NYX-2925.

Conclusions: NYX-2925 (1-10 mg/kg) improves sleep in rats and is analgesic in multiple preclinical models of chronic and neuropathic pain. These data suggest that NYX-2925 could enhance synaptic plasticity via improved sleep quality. The decreases in delta power during wake suggest that NYX-2925 may also improve vigilance during wake. The facilitation of NREM sleep by NYX-2925 demonstrates its potential to alleviate a core symptom of neuropathic pain and also serve as a biomarker for drug effects.

Keywords: NMDA Receptor, Sleep, Biomarker, Novel Therapeutics

Disclosure: Aptinyx Inc., Employee

W143. Parent Validation of the Autism Behavior Inventory – a Cognitive Debriefing Study

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Background: Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental disorder with no medical treatments approved for core symptoms of social communication deficits or restricted repetitive behaviors. Few rating scales exist to measure symptom severity and change for use in clinical trials, particularly over a brief time period. The Autism Behavior Inventory (ABI), a web-based observer reported outcome scale that measures the core and associated features of ASD, was developed in alignment with Food and Drug Administration (FDA) PRO Guidance (FDA 2009) to address this measurement need (Bangerter et al., 2017). To provide further evidence for the validity of the ABI, cognitive interviews were conducted with participants who were parents or caregivers of verbal or minimally/non-verbal children, adolescents, and adults with ASD (aged 3 years to adult).

Methods: This non-interventional, qualitative study involved cognitive interviews conducted with participants via a web-based platform. The study aligned with current recommendations for establishing and reporting the content validity of PRO instruments to be used to support label claims (Patrick et al. 2007; FDA 2009). Participants were drawn from a community sample via available databases, ASD advocacy support group networks, and patient panels with a broad range of educational level, occupation, and racial/ethnic representation. The target participant sample was stratified by verbal functioning level (minimal vs. 'higher'), grouped by age of affected individual and reflected the heterogeneity of ASD. Age bands included participants who cared for individuals with ASD aged 3-11 years (n~20), versus adolescents or adults (12-17, or 18 + years, n~20).

Inclusion criteria required that interviewees be a parent of an individual with ASD age 3 years to adult and confirm the individual with ASD has been diagnosed for > 6 months by a qualified clinician using DSM IV/V criteria. The parent must spend > 3 h/day with the person with ASD, be able to read and understand English, be willing to participate in an interview lasting up to 90 minutes and provide informed consent.

Participants provided electronic informed consent which was verbally confirmed by trained research interviewers prior to the interview. Cognitive interviews used the think-aloud approach (Willis 2015), and were conducted using a discussion guide with semi-structured questions to assess respondent perspectives on the ABI's content validity and their understanding of the instrument, including: (1) item clarity and relevance (including item example relevance); (2) item interpretation; (3) comprehensiveness of the instrument; (4) appropriateness of the format, response scales, and recall period; and (5) clarity of instructions. Audio-recordings of the interviews were collected and transcribed for data analysis.

Results: Fifty participants (n = 44 females, 88%) completed cognitive interviews with the ABI. Parents' average age was 42.3 years (+ 8.88). The majority of parents were married (n = 26, 52%), had some college (n = 26, 52%) or a college degree (n = 15, 30%), and were employed full time (n = 24, 48%), part time (n = 8, 16%) or were homemakers (n = 16, 32%). Their children/adults with ASD were on average 12.4 years (+ 8.15). The majority were either White (60%) or African American (28%). About half had fluent language ('speaks in full sentences', n = 21, 42%), and the majority received their diagnosis between the ages of 2 and 3 years (n = 28, 56%). The most frequent psychiatric comorbidity was ADD/ADHD (n = 12, 24%).

Parents understood almost all ABI items without the need for explanation or additional examples (ie, "all/most items are clear") and were able to select an appropriate response from the options available. The first 38 interviews tested a 70-item version of the ABI. Following these interviews, the instructions for scale completion were simplified and the number of items was reduced from 70 to 62, based on parent feedback and the review consensus process from the research team. Descriptive examples for each item were retained as parents reported that they were useful. Ten items or examples were expanded or reworded, for one of three reasons: 1) several items had potential for

misunderstanding or differences in interpretation; 2) a few items were revised to be appropriate across all age groups (e.g., "items 29 and 49 didn't apply to my son because he is only 5"), and 3) items were perceived by caregivers as very similar in meaning. The final revised 62-item scale was presented to 12 more parents; this group readily understood the instructions and item content in the final version, and further confirmed the utility of suggestions from the initial 38 parent interviews.

Conclusions: Cognitive interviews with parents or caregivers from a diverse sample of individuals with ASD confirm the validity and utility of the ABI to assess the heterogeneous core and associated symptoms of ASD. These findings further confirm parent or caregiver feedback received during initial item development and psychometric evaluation of the validity and reliability of the ABI in ASD. Further clinical studies will elucidate the utility of the ABI in measuring symptom change over time.

Keywords: Autism Spectrum Disorder, Rating Scales, CNS Clinical Trials

Disclosure: Johnson & Johnson, Employee, Johnson & Johnson, Stock / Equity

W144. Increased Incidence of Diseases of the Basal Ganglia and Cerebellum, Including Parkinson's Disease, in Patients With a History of Attention Deficit Hyperactivity Disorder

Abstract not included.

W145. Preliminary PET/MR Imaging of Class I Histone Deacetylase Expression and Grey Matter Volume Loss in Huntington's Disease

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Background: Huntington's disease (HD) is a late onset neurodegenerative disease characterized by cognitive decline, psychiatric symptoms, and progressive motor dysfunction. The disease results from an autosomal dominant mutation of the HD gene, huntingtin (htt). A polymorphic trinucleotide repeat sequence (CAGn) is expanded, leading to translation of an expanded polyglutamine sequence. Proteolysis of mutant htt sets off a cascade of damaging and compensatory processes that lead to fragile, atrophic, dysfunctional neurons. Striatal atrophy is a feature of HD with greater cortical atrophy as disease progresses [1].

Multiple studies have reported differences in epigenetic markers as well as in the expression of genes in distinct regions of postmortem tissue. Genetic mouse models support an important role of these markers in the pathogenesis of HD [2,3]. Histone deacetylases (HDACs) are a family of enzymes grouped by class that regulate gene expression by modifying chromatin in human DNA. HDACs regulate neuronal death and survival and play a role in neurodegenerative pathologies, depending on the class [3]. The primary goal of this preliminary study is to measure regional changes in HDAC expression and gray matter volume in vivo in HD patients using [11 C]Martinostat, a PET radioligand selective for class I HDACs (isoforms 1-3), which are associated with regulating neuroplasticity and cognition [4].

Methods: Subjects: Fifteen individuals were studied, seven healthy control subjects (57 ± 4.9 years, 4 female) and eight HD patients (60.9 ± 6.2 years, 3 female). Disease burden was calculated for all HD patients, based on the method of Tabrizi et al. (2009) [5] to estimate each individual's lifetime exposure to mutant htt at any age before and after motor onset.

Neuroimaging: All subjects underwent simultaneous PET/MR imaging (Siemens BrainPET) after administration of 5.39 ± 0.31 mCi (controls) and 4.97 ± 0.13 mCi (patients) of [11 C]Martinostat. PET data were acquired 60-90 minutes post-injection and a standardized uptake value tissue ratio (SUVR) image was generated using whole brain SUV as reference. T1-weighted MPRAGE MRI data were acquired for PET/MR co-registration and regional parcellation was performed using Freesurfer Version 6.0 [6] for several gray matter (GM) and white matter (WM) volumes-of-interest. MRI volumes were normalized to intracranial volume (ICV).

Statistical Analysis: In addition to descriptive statistics, we applied Wilcoxon rank tests to compare group means and Spearman rank correlations to examine relationships between study outcomes (i.e., MR volumes, PET SUVR and disease burden). Regression was also applied to explore sex- and age-related effects. No corrections were made for multiple comparisons.

Results: The regional HD MR volumetric measures are consistent with the literature regarding HD pathology and atrophy [7]. Statistically significant ($p < 0.05$) group differences were found in striatum for both the [11 C]Martinostat PET SUVR and the MR volumes, most notably for caudate (Cohen's d for PET SUVR: 2.57 and MR volume: 2.71) and pallidum (Cohen's d for PET SUVR: 2.90 and MR volume: 4.24) regions. The PET SUVR was about 20% lower and MR volume was nearly 60% lower in the caudate region of patients compared to controls. Conversely, while pallidum MR volume was nearly 50% lower in HD patients than controls, the HD SUVR was about 10% higher. The HD SUVR was slightly higher (3-7%) for white matter rich areas of brainstem and cortical white matter that corresponded to about 15% lower HD MRvol values (relative to controls). Group differences in the neuroimaging measures were not significant in the cortical areas explored. Disease burden was weakly correlated to SUVR in the volumes measured; R2 values ranged from 0.002 (cortical white matter) to 0.3117 (caudate). Regression analyses did not suggest age or sex effects.

Conclusions: This preliminary study suggests HDAC expression may be differentially regulated in HD brain areas impacted early in the disease process and supports further use of [11 C]Martinostat PET to study epigenetic mechanisms in Huntington's Disease. The results further suggest that the [11 C]Martinostat PET results are not solely driven by age- and/or disease-related atrophy. Limitations of this study include a small sample size and the need to further consider motion and atrophy effects. Further studies with larger sample sizes are warranted, especially including pre-manifest HD patients to more accurately cover the disease spectrum.

Keywords: Huntington's Disease, HDAC, Simultaneous PET-MR

Disclosure: Nothing to disclose.

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W146. Preliminary Evaluation of the Effectiveness, Safety, and Dose Response of Cannabinoids in the Treatment of Chronic Pain

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Background: Interest in cannabis-based medicines has exploded in recent years. This is evidenced by the 29 states and 3 US districts that have public medical cannabis programs. Schedule

1 status, variability in product potency, and heterogeneity in the design of state programs has made clinical studies difficult. New York State's (NYS) program has stringent legislation requiring good manufacturing practices, reliable drug pedigree, and consistent product potency. The state requires analysis of 9 cannabinoids and accurate reporting of tetrahydrocannabinol (THC) and cannabidiol (CBD) content on the product labels. The quality and consistency of the product, along with the required monitoring of controlled substances allowed us to evaluate the effectiveness of cannabinoids in the treatment of chronic pain.

Methods: Institution Review Board approval was given to conduct this retrospective, mirror-image study that investigated the effectiveness of cannabinoids in patients suffering from chronic pain. All patients meeting inclusion criteria and no exclusion criteria were included and served as their own controls. Ambulatory patients were evaluated at baseline and every 3 months to assess response and monitor therapy. The primary outcome was to compare Pain Quality Assessment Scale (PQAS) scores at baseline and at 3- and 6-months post-therapy. Secondary outcomes included comparing opioid consumption pre- and post-therapy and characterizing daily dose of THC and CBD at 1 and 3 months. Euphoria was assessed using the 5-item Drug Effect Questionnaire (5-DEQ) and tolerability was assessed using an adverse effects checklist.

Results: 53 ambulatory patients with a diagnosis of chronic pain were included in this evaluation. Patient demographics included: age 52 + /- 10, 98% Caucasian, 2% African American, 31 females, 22 males, duration of illness 18 + /- 9 years. Clinical outcome: PQAS Paroxysmal (Pre 7.02 – Post 2.12, $P < .0001$), Surface (Pre 5.20 – Post 1.49, $P < .0001$), Deep (Pre 6.67 – Post 3.13, $P < .0001$), Unpleasant (Pre "miserable" – Post "annoying", $P < .0001$). Opioid consumption: morphine equivalents (Pre 79.94–Post 18.53, $P < .05$). Daily dose of THC and CBD: 1 month 13.0 mg THC and 6.2 mg CBD, 3 months 10.6 mg THC and 4.5 mg CBD. Side effects were reported in 17% of subjects. No subjects reported euphoria after 6 months therapy.

Conclusions: Due to study limitations, these results may not be applicable to the general population. The present study provides evidence that cannabinoids are an effective and well-tolerated treatment for chronic pain. In addition, the observed analgesic dose appears to be lower than the euphoric dose in our subjects. Additional studies investigating how plasma cannabinoid levels correlate with analgesic effects would be illuminating. A large trial or a randomized placebo-controlled clinical trial is warranted to further evaluate the role of cannabinoids in the treatment of chronic pain.

Keywords: Cannabinoids, Chronic Pain, Chronic Pain Treatment, Cannabis, Cannabinoid

Disclosure: Nothing to disclose.

W147. The Discovery of Dopamine D1 Positive Allosteric Modulators for the Treatment of Neuro-Psychiatric Disorders

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Background: The dopamine D1 receptor plays a critical role to maintain motor activity, reward and higher cognitive functions including working memory, attention and executive function (Goldman-Rakic et al., 2004). Increased cortical D1 activity could address critical unmet medical needs in many neuro-psychiatric disorders in particular cognitive impairment. While selective D1 agonists are active in animal models relevant to clinical applications for neuro-psychiatric disorders, the development of D1 agonists for clinical use has not been successful due to issues with receptor desensitization, poor drug like properties, or dose limiting side effects (eg Arnsten et al 2017, but see Gray et al., 2018).

We tested the hypothesis that a dopamine D1 positive allosteric modulator (D1PAM) could address some of the issues associated with D1 agonists and offer a more physiological approach to activation of D1 receptors with temporal and spatial resolution related to endogenous dopamine release (cf. Svensson et al., 2017 and Bruns et al., 2018).

Methods: In vitro testing for potentiation of dopamine induced increase in cAMP was performed using cloned human D1 cells. Mutagenesis and D1/D5 chimera studies identified a new binding site for D1PAM. In vivo testing was done in human D1 receptor knock-in (hD1KI) mice due to a significant rodent-human species difference in binding of D1PAM. Novel preclinical data will be presented for the clinical candidate D1PAM LY3154207 and for the D1PAM DETQ with comparative data for selective receptor dopamine D1 receptor agonists.

Results: The D1PAM DETQ showed high alpha-shift and dopamine D1 selectivity. Studies with chimeric receptors identified a novel allosteric binding site at the second intracellular loop. In vivo DETQ increased locomotor activity in hD1KI mice over a wide dose range without evidence for inverted U-shaped dose-response and also enhanced wakefulness in a sleep study. DETQ reversed hypo-activity caused by pre-treatment with a low dose of the dopamine depleting agent reserpine and acted synergistically with L-DOPA to reverse the akinesia seen with a high dose of reserpine. Microdialysis studies showed that DETQ increases release of acetylcholine in the hippocampus where it had an additive effect together with the acetylcholinesterase inhibitor rivastigmine. DETQ increased phosphorylation of CREB and the AMPA receptor GluR1 in the brain ex vivo suggesting enhanced synaptic plasticity. Testing in the novel object recognition model for cognition showed dose relate reversal of PCP induced deficits with DETQ.

Conclusions: We conclude that preclinical data support further development of D1PAMs for neuro-psychiatric disorders. This includes LY3154207 which recently entered phase 2 studies in Parkinson's disease dementia.

Keywords: D1 dopamine receptors, Positive Allosteric Modulators, Drug Discovery - New Approaches, Synaptic plasticity, Cognition

Disclosure: Eli Lilly, Employee, Eli Lilly, Stock / Equity

W148. Acute Behavioral Effects of α2/α3-Subtype Selective Gabaa Receptor Positive Allosteric Modulators in Rats

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Background: Spinal GABAA receptors are crucial modulators of pain processing. However, nonselective GABAA receptor positive allosteric modulators (PAMs) are not suitable for clinical pain control due to various adverse effects unrelated to analgesia. Genetic and pharmacological studies have demonstrated that while α2/α3 subunits of GABAA receptors mediate pain processing, α1 subunit-containing GABAA receptors mediate sedative and abuse related effects. Therefore, α2/α3 subtype-selective GABAA receptor PAMs have received increasing attention as potential analgesics. This study sought to examine the behavioral effects of two α2/α3 subtype-selective GABAA receptor PAMs: KRM-II-81 and NS16085.

Methods: The antinociceptive effects of KRM-II-81, and NS16085, were examined using a rat model of inflammatory pain (complete Freund's adjuvant) and a rat model of neuropathic pain (chronic constriction injury). Two pain assays, mechanical and thermal nociception (as measured by von Frey and Hargreaves tests, respectively) were conducted in both pain models. In pain-free rats, rate-suppressing effects (food-maintained operant responding), and muscle-relaxant activity (horizontal wire test), were assessed to study the side-effect profiles of KRM-II-81 and NS16085. These effects were compared to the side-effect profile of classical benzodiazepine, midazolam.

Results: Both KRM-II-81 and NS16085 dose-dependently attenuated mechanical nociception in both inflammatory and neuropathic pain states. Contrastingly, neither KRM-II-81 nor NS16085 attenuated thermal nociception. In the procedure of food-maintained operant responding, KRM-II-81 and NS16085 did not significantly decrease the response rate at doses that produced maximal antinociception. However, midazolam significantly reduced the response rate at doses that attenuated mechanical nociception. In the horizontal wire test, within the dose range that produced antinociception, only midazolam dose-dependently increased the percentage of rats unable to grasp the wire, indicating muscle-relaxant activity. These behavioral effects can be attenuated by benzodiazepine receptor antagonist flumazenil, confirming that the behavioral effects of these subtype-selective GABAA PAMs are mediated through the benzodiazepine site of GABAA receptors.

Conclusions: Taken together, while the nonselective midazolam produced antinociceptive, rate-suppressing, and muscle-relaxant activity at similar doses, both subtype-selective GABAA receptor PAMs selectively produced antinociceptive effects. Collectively, these data support the notion of α2/α3-subtype selective GABAA PAMs as a novel class of analgesics.

Keywords: GABAA Receptor Positive Allosteric Modulator, Pain, In Vivo

Disclosure: Nothing to disclose.

W149. Modulation of Serotonin Levels During Development Produce Long-Lasting Changes in Dopaminergic Function

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Background: Serotonin (5HT) levels peak during the perinatal phase in rodents, when changes in serotonergic tone (e.g. by stress, maternal abuse, pharmaceutical drugs or inflammation) may derail typical brain development and cause enduring behavioral deficits. Previous studies have shown that perinatal exposure to selective-serotonin-reuptake-inhibitors (SSRIs, e.g. fluoxetine) lead to behavioral deficits in the adult progeny that include social interaction deficits and anxiety-like phenotypes. To study the functional and structural deficits behind the altered behaviors we focused on the interaction between serotonergic and dopaminergic systems in mice. 5HT cells in the Dorsal Raphe (DR) project to a strong disynaptic DR > Ventral Tegmental Area (VTA) > Nucleus Accumbens (NAc) circuit. VTA DA neurons have a critical role in reward prediction, motivation and arousal, and changes in the VTA > NAc circuit are associated with behavioral impairments in mood disorders. The primacy of the serotonergic system in modulating DA development is suggested by the directionality of projections in this circuit (DR > VTA) and by the DA system developing later than the 5HT system.

Methods: Using a combination of microdialysis, optogenetics, fiber photometry and behavioral testing we tested the effects of perinatal exposure to fluoxetine (PN-FLX) on DA system function in the adult. Between 10 to 15 mice per group, male and female, were administered with saline or fluoxetine (10 mg/kg IP) from P2 to P11. When the mice reached 8 weeks of age they were tested in social interaction, operant conditioning, amphetamine response and response to a sucrose reward.

Results: We have found that PN-FLX mice present a hypodopaminergic phenotype. PN-FLX mice showed a blunted activation of DA cells in response to sucrose intake, measured by GCAMP6 activation in VTA-DA cells. Furthermore, DA levels measured by microdialysis in the striatum, after an amphetamine challenge, were lower in PN-FLX mice compared to saline-treated controls. Consistent with a hypodopaminergic phenotype, PN-FLX mice presented deficits in motivation (lower break point the progressive ratio) and social interaction.

Conclusions: This study provides new insights on how the serotonergic system modulates the dopaminergic system during development, with broad implications for mood disorders, autism, schizophrenia and developmental neuroscience.

Keywords: Serotonin, Dopamine, Sensitive Period

Disclosure: Nothing to disclose.

W150. Can the Brief Smell Identification Test Be Used to Identify Patients With Cognitive Attributes of Early Alzheimer's Disease in Patients With Late Life Depression?

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Background: Background: Impaired odor identification is associated with memory decline and progression to dementia. However, most of the research on olfaction has been in non-depressed samples at risk for Alzheimer's Disease. Cognitive Impairment is common in late life depression, but attribution of cause is complicated by the presence of multiple potential factors. Our objective was to determine the frequency of impaired smell identification in late life depression and if impaired olfaction is associated with impaired memory scores in late life depression, which might suggest the presence of early Alzheimer's Disease.

Methods: Methods: Subjects were enrolled in the ADNI-Depression study and a Multi-Modal imaging study of Problem-Solving Therapy in Late Life Depression. Inclusion criteria for the study were Major Depressive Disorder of six weeks duration determined with a Structured Clinical Interview (SCID), and a 17-item Hamilton Depression Rating Scale score of 15 or greater. Exclusion criteria were a Mini Mental State Score (MMSE) < 25 or a clinical diagnosis of dementia; another psychiatric disorder (except for simple phobia or generalized anxiety disorder); a neurological disorder such as Parkinson's Disease, stroke, or traumatic brain injury, a contraindication to Magnetic Resonance Imaging; or current medications likely to impair cognition. All subjects received a comprehensive neuropsychological test battery. Olfaction was tested with a 12-item Brief Smell Identification Test (BSIT) (Sensonics, Inc 2001). A BSIT score below the 5th percentile was considered abnormal. BSIT scale scores were correlated with the patient's perception of memory decline on the Cognitive Change Index. Chi square analyses were performed to assess the relationship of abnormal /normal BSIT scores with impairment (scale score < 7) on the Hopkins Verbal Learning Test-delayed memory (HVLT-DM), the Rey Auditory Verbal Learning Test-delayed memory RAVLT-DM), and the Wechsler Memory Scale III-Logical Memory (WMS III-LM), and with the presence/absence of amnestic

MCI. MCI was defined by impaired memory on one of the 3 delayed memory scales and impairment in one other cognitive domain using age-adjusted scale scores.

Results: Results: The sample included 98 subjects (55 men and 43 women). Mean age (SD) was 71.6 (5.7), mean level of education 16.6 years (2.1), mean MMSE 29.0 (1.1), mean HDRS17 = 19.1 (3.4). Seven of the 98 subjects had BSIT scores below the 5th percentile. Among MCI patients 2/16 (12.5%) had an impaired BSIT while in non-MCI patients 5/82 or 6.1% were impaired. The correlation of the BSIT with the subjective perception of memory decline (Cognitive Change Index) was r = .02, df = 65, p = .87. The association of the BSIT with the HVLT was X2 = 3.46, df = 1, p = .06, with the RAVLT was X2 = .03, df = 1, p = .85, with the WMS III-LM was X2 = 1.21, df = 1, p = .27, and with the presence or absence of amnestic MCI was X2 = .83, df = 1, p = .36.

Conclusions: In this sample impaired olfaction, tested by the BSIT, was not associated with delayed memory impairment, patients' perception of memory decline, or with amnestic Mild Cognitive Impairment. One of the limitations of the study is that in these subjects, selected for depression and without a clinical diagnosis of dementia and with a MMSE ≥ 25, only 7 had BSIT scores in the abnormal range while 5 would be expected by chance. Other implications and limitations of the findings will be discussed. Supported by R01 MH0977669: (PI:Mackin), R01 MH101472 (PI:Mackin); UCSF Epstein Fund (Nelson)

Keywords: Late-life Depression, Cognition, Olfaction

Disclosure: Janssen, Consultant, Eisai, Consultant, Assurex, Advisory Board, UpToDate, Royalties

W151. Getting to Precision Medicine in Antipsychotic-Induced Weight Gain: A "Multi-Omic" Approach

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Background: Genome-wide association studies (GWAS) have successfully identified many genomic regions associated with obesity, fat deposition, and antipsychotic (AP)-induced weight gain (AIWG), but the combination of all known single nucleotide polymorphisms (SNPs) explains only a small fraction of AP-induced weight gain. Moreover, no studies have evaluated AP-induced changes specifically in adiposity, which is the most likely driver of cardiometabolic risk (CMR). Patient DNA analysis using array-based genotyping and exome sequencing can identify rare, even unique variants influencing treatment response. However, alone they are insufficient to establish causal links between genotype and phenotype. Unbiased functional approaches like metabolomics and genomic screening using CRISPRi are increasingly used in precision medicine. Here, we combine these methods with patient DNA analysis to validate genomic contributions to AP-induced increases in adiposity. We present a pilot version of our patient-to-gene pharmacogenomics approach: 1) application of a statistical method developed by Helena Kraemer to combine existing clinical and GWAS data to generate a multiple moderator of antipsychotic-induced weight gain (AIWG) 2) functional validation of genomic variants of psychotropic medication response using CRISPRi and 3) Transcriptional and metabolomic profiling experiments to identify potential target mechanisms for AP-induced gains in adiposity and associated CMR.

Methods: Experiment 1: Depressed older adults aged ≥ 60 years with non-response to venlafaxine were randomized to 12 weeks of aripiprazole augmentation (n = 91) or placebo (n = 90). Change in total body adiposity was quantified using a dual energy x-ray absorptiometry (DEXA) at baseline and 12 weeks. We selected 20 independent moderators of total body fat gain -- 10 clinical and 10 genetic -- and combined them to generate an effect size of a single weighted composite moderator to predict individuals who gained fat during aripiprazole augmentation.

Experiment 2: As a test of the generalizability and efficacy of our approach, we applied the CRISPRi technique using a human hematopoietic cell line (K562) to investigate several mechanistically distinct, commonly prescribed psychotropic drugs – fluoxetine and lithium.

Experiment 3: To pursue molecular mechanisms for AP-induced fat gain, we performed RNAseq-based transcriptional profiling and metabolomic profiling, using APs with differential fat gain potential: olanzapine (high) and aripriprazole (low).

Results: Experiment 1: The combined clinical and genetic moderator (Mcg) Kraemer effect size was 0.57. The largest individual moderators were mental health-related quality of life (0.21) and the SNP encoding for the 5-hydroxytryptamine 2 C (5HT2C) receptor (0.14).

Experiment 2: Statistically significant gene hits with lithium included SLC7A7, DEPDC5, Tuberous Sclerosis Complex 1 (TSC1), and SLC1A5. These data suggest that lithium might meaningfully alter the activities of several sodium-dependent transporters. CRISPRi screening with fluoxetine identified the insulin pathway component, PTEN, as the top hit.

Experiment 3: The pathways that were selectively and differentially expressed by olanzapine include cholesterol and isoprenoid biosynthetic processes. In metabolomics analysis, we detected a cluster of metabolites that were selectively regulated by aripriprazole treatment including the amino acids, valine and cysteine and the sugar mannose.

Conclusions: Experiment 1: A multiple moderator analytic approach, using data from a randomized clinical trial, can be applied to existing gold standard and genetic data to identify patients at risk for adverse medication effects.

Experiment 2: Cellular metabolism is a key target of psychiatric drugs, suggesting that CRISPRi methodology can identify and functionally validate effects of drug exposure on genes of interest.

Experiment 3: These results are consistent with several reports in patients taking olanzapine, including in children, where blood cholesterol levels positively correlated with fat gain. Metabolomics analyses suggest that downregulated amino acid levels might be protective against fat gain with aripiprazole, while increased production of mannose may be associated with decreases in insulin sensitivity with aripiprazole.

As a starting point towards developing personalized approaches to AP-induced increases in adiposity and related increases in CMR, we have demonstrated the feasibility and utility of a "multi-omic" patient-to-gene pharmacogenomics pipeline. Future efforts are underway to utilize additional unbiased genomic approaches, including imputation and exome sequencing in larger samples, in an effort to characterize the full genomic contribution to AP-induced increases in adiposity. The final step in the process will be to employ CRISPRi/a assays generating rapid feedback on the functional nature of candidate variants/regions and improving our ability to detect truly causal genetic variants for AP-induced gains in adiposity.

Keywords: Antipsychotic Unduced Weight Gain, Cardiometabolic Risk, Pharmacogenomics

Disclosure: Otsuka America, Inc., Grant, Alkermes, Grant

W152. Astrocyte Neuroimmune Responses to Opioids

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Background: The opioid epidemic is a massive public health problem in the United States. The intertwined misuse of prescription opioids with the emergence of extremely potent fentanyl derivatives has triggered even greater concerns. The incidence of repeated drug overdose events indicates a problematic use pattern consistent with the development of opioid use disorder (OUD).

Increasing evidence suggest that neuroimmune adaptations form a vital role in the neuropathology and behavioral indicators of OUD. Peripherally derived immune factors may influence increased inflammatory cytokine/chemokine expression, reactive gliosis, antigen-presentation markers and NF-κB transcriptional activity within the prefrontal cortex (PFC) and nucleus accumbens (NAc), profoundly influencing neuroplasticity that reinforces OUD. Neuroimmune signaling is categorized as anti- or pro-inflammatory. Interestingly, pro-inflammatory cytokines, such as interleukin (IL)-8, tumor necrosis factor (TNF)-α and IL-1β aggravate deficits in neuroplasticity, while anti-inflammatory cytokines, such as IL-10, can boost neuroplasticity. In parallel, exogenous opioid administration induces pro-inflammatory cytokine expression, via microglia toll-like receptor (TLR)4 signaling and may contribute to the bolstering properties of OUD. Alternatively, anti-inflammatory signaling attenuates reinforcing effects of opioids as demonstrated by an increase of anti-inflammatory production, IL-10 in the NAc, thereby reducing opioid self-administration.

Astrocytes, the most abundant cell in the central nervous system, potently respond to foreign substances by generating and releasing inflammatory cytokines and chemokines. Astrocyte-induced neuroimmune adaptations transpire across a scattered set of neural circuits and contribute to assorted outcomes related with opioid exposure and dependence, including participation in the development of plasticity of dendritic spines, synapses and neurotransmission. Reactive astrocyte phenotypes during opioid-dependent states may drive the behavioral transformations that remodel limbic-corticostriatal circuitry and lead to opioid dependence and addiction.

The exact mechanisms of astrocyte-induced neuroimmune adaptations during OUD remain elusive. Astrocytes express a plethora of PRRs that may dictate these neuroimmune alterations, including cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING), canonically activated by pathogen or self-genetic material, and mitochondrial antiviral signaling (MAVS) protein, regulated by changes in mitochondrial equilibrium. We investigate the role of MAVS and STING in activating fentanyl-induced inflammation in astrocytes, in vitro and ex vivo.

Our preliminary studies demonstrate that fentanyl results in an activated astrocyte phenotype and increases astrocyte pro-inflammatory cytokine levels. We hypothesize that fentanyl triggers MAVS-STING signalsome pathways to activate astrocyte innate immune signaling; thereby providing therapeutic targets to attenuate OUD.

Methods: Primary human astrocytes were maintained at 5% CO2 at 37°C. Primary rat astrocytes were isolated from the PFC and whole brain and sustained in astrocyte conditioned media (DMEM, 10% FBS, 1% PSN) and maintained at 5% CO2 at 37°C. Primary astrocytes were treated with escalating doses of fentanyl or saline for 24 h. Protein, RNA and supernatants were isolated from activated astrocytes and used for real-time PCR, immunoblotting, and ELISAs. Astrocytes were fixed in 1:1 Acetone:Methanol and used for immunocytochemistry and confocal microscopy. Astrocytes were MOCK-, siCON, siSTING and siMAVS-transfected and cultured in 6 well plates for RNA extraction. The rat brain tissue was collected from adult male, Sprague-Dawley rats that underwent several rounds of drug testing. All rodent experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (National Research Council) and with the approval of the Institutional Animal Care and Use Committee at UTMB.

Results: We demonstrate that fentanyl activates astrocyte innate immune signal transduction pathways and increases proinflammatory cytokine production. Specifically, fentanyl (100 nM) increased IL6 and IL8 by approximately 4-fold (***$p < 0.001$), while decreasing anti-inflammatory cytokine, IL10, by approximately 2-fold (***$p < 0.001$). In parallel, we show that fentanyl alters MAVS and STING expression, activation and subcellular localization. Lastly, we validate that MAVS and STING play a role in mediating fentanyl-induced neuroinflammatory outcomes.

Conclusions: Taken together, our in vitro and ex vivo data demonstrates that opioids activate astrocyte-induced neuroimmune signaling pathways. We hope to address the role of astrocyte-mediated neuroinflammation in the aberrant, impulsive, and compulsive behaviors that characterize the neurobiology of opioid addiction and by identifying novel mechanistic targets of opioid-induced neuroinflammation we may be able to identify therapies to attenuate OUD.

Keywords: Opioid Abuse, Astrocyte, Neuroinflammation

Disclosure: Nothing to disclose.

W153. Doublecortin (DCX) Expression Can be Regulated Independently of the Number of Adult-Born Granule Cells

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Background: In the adult dentate gyrus (DG) of the hippocampus, the microtubule-associated protein doublecortin (DCX) is exclusively expressed in immature neurons from 1 to 4 weeks of age. DCX has been widely used as an immature neuronal marker that reliably reflects the levels of adult hippocampal neurogenesis (AHN). However, it has been recently suggested that the survival and maturation of adult-generated hippocampal neurons does not require DCX1. Thus, we investigated whether DCX expression in the mouse DG can be regulated independently from levels of AHN under various conditions including antidepressant treatment or inflammation.

Methods: AHN, including DCX expression was first evaluated using a chronic antidepressant treatment (fluoxetine, 18 mg/kg/day) in a mouse model of depression based on elevation of glucocorticoids in sham or irradiated animals (CORT model, $n = 12/15$ per group). Because of the importance of beta-arrestin 2 (b-arr 2) for the effects of antidepressants, we also studied the neurogenic consequences of its deletion in comparison to wild-type treated animals ($n = 3/5$ per group). Then to provide further evidences that DCX is regulated independently from AHN, a dorsal injection of a pro-inflammatory lipopolysaccharide (LPS, 1 mg/ul) on one side of the hippocampus were applied in male C57BL/6JRj mice, 24 h, 3 days or 7 days before sacrifice ($n = 12/15$ per group). Finally, we evaluated whether fluoxetine–increased DCX expression is related to microRNA (miR) variation in the mouse CORT model. A one- or two-way ANOVAs were applied as appropriate, followed by Fisher's PLSD post-hoc test.

Results: In the mouse corticosterone model of anxiety/depression, we showed that chronic fluoxetine increased DCX expression to a larger extent than the number of surviving adult-born granule cells (GCs). We also showed with X-irradiation or pharmacogenetic ablation of AHN that the increase in DCX expression under fluoxetine treatment was entirely due to adult-born GCs rather than to mature GCs. Moreover, using □-arr2 knockout mice, we showed that fluoxetine increased massively DCX expression without affecting the proliferation and survival of adult-born GCs. Then, injecting LPS in the mouse dorsal DG, we showed a large reduction in DCX expression in comparison to a more modest reduction in the survival of adult-born GCs, 24 h, 3- and 7-days post-injections. Finally, we demonstrated that chronic fluoxetine-induced DCX expression is associated with changes in hippocampal miR expression (18a5, 22a3, 34a3, 128).

Conclusions: All together, these findings show that DCX expression is regulated independently of the levels of AHN and should therefore be used very cautiously as an index for numbers of immature adult-born hippocampal neurons.

Keywords: Adult Hippocampal Neurogenesis, Antidepressant, Doublecortin, miRNA, Beta Arrestin 2

Disclosure: Lundbeck, Advisory Board (Spouse)

W154. Abnormal Amygdala-Striatal Network Relates to Apathy in Myotonic Dystrophy 1

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Background: Apathy is a known feature of Myotonic Dystrophy 1 (DM1); however, few studies have investigated the possible mechanisms. The amygdala-striatal circuitry is known to be involved in motivational salience, and dysregulation of this circuit may be associated with apathy in DM1.

Methods: The sample included 42 controls (24 females; 18 males) and 44 individuals with DM1 (30 females; 14 males) who were on average 45 years old at the time of evaluation (SD = 13). Apathy was assessed using the AES Evaluation Scale. Neuroimages were acquired with 3 T Siemens or GE scanner and images were processed with BrainsTools. Linear models were conducted to assess if apathy scores can be explained by amygdala and caudate volume, corrected for intracranial volume. Group and sex were added as covariates.

Results: The DM1 group exhibited significantly higher apathy scores compared with controls, which was evident in self-rated scores ($t(80) = 3.9$, $p < 0.001$) and proxy-rated scores ($t(28) = 3.9$, $p < 0.001$). Apathy score was significantly associated with abnormalities in amygdala and caudate volume in individuals with DM1, but not controls: proportionally smaller amygdala was associated with greater apathy ($t(72) = -2.4$, $p < 0.05$), and proportionally larger caudate was associated with greater apathy ($t(72) = 2.4$, $p < 0.05$).

Conclusions: Apathy in DM1 may be associated with dysregulations in the amygdala-striatal circuitry. Regional neuroimaging analyses suggest that the amygdala is enlarged in DM1, perhaps to compensate dysregulation of the amygdala-striatal circuitry.

Keywords: Apathy, Amygdala-Based Networks, Neuroimaging

Disclosure: Nothing to disclose.

W155. Distinct Cortical-Amygdala Projections Drive Reward Value Encoding and Retrieval

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Background: To make adaptive decisions we must cast ourselves into the future and consider the outcomes of our potential choices. This prospective consideration is informed by our memories. For example, the memory of the value of an anticipated rewarding event is crucial information in the decision to engage in its pursuit. The networks responsible for encoding and retrieval this value are largely unknown.

Methods: We used glutamate biosensors, pharmacological, chemogenetic, and optogenetic manipulations coupled with a behavioral task designed to examine the encoding and retrieval of need-state dependent value of a food reward.

Results: We found that basolateral amygdala (BLA) glutamatergic activity tracks and mediates both the encoding and retrieval of the hunger-state-dependent value of a palatable food reward. The orbitofrontal cortex (OFC) supports the BLA in these processes. Critically, the function of the ventrolateral (lOFC) and medial (mOFC) OFC->BLA projections was found to be doubly dissociable. Whereas activity in lOFC->BLA projections is necessary for and sufficient to drive encoding of a positive change in the value of a reward, mOFC->BLA projections are necessary and sufficient for retrieving this value from memory to guide reward pursuit.

Conclusions: These data reveal a new circuit for adaptive reward valuation and pursuit and provide mechanistic insight into the dysfunction in these processes that characterizes myriad psychiatric diseases.

Keywords: Amygdala, Orbitofrontal Cortex, Optogenetics, Chemogenetics, Reward

Disclosure: Nothing to disclose.

W156. Attention Deficit Hyperactivity Disorder (ADHD) Genetic Risk and Striatal Systems Function

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Background: Attention deficit hyperactivity disorder (ADHD) is a prevalent condition (Thomas et al, 2015) of unknown etiology but substantial heritability (Larsson et al, 2013). First-line treatment for ADHD focuses on stimulants that enhance synaptic dopaminergic tone, and dysfunction in dopamine-dependent frontostriatal networks has been well demonstrated in patients. Prior work has found abnormalities of striatal presynaptic dopamine function in drug naïve ADHD cohorts (Cherkasova et al, 2013; Ludolph et al, 2008), and resting state striatal relays may be an important clinical target (Rubia et al, 2011). Candidate gene association studies have implicated variants affecting dopamine signaling (Hawi et al, 2015), but a recent genome-wide association study meta-analysis has identified a dozen risk loci that substantially broaden the known molecular architecture underlying this disorder (Demontis et al, 2017). Whether this molecular architecture in aggregate has functional relevance to striatal physiology is unknown but may

have importance for understanding how genetic risk leads to clinical impairment.

Methods: One-hundred and fifty-eight healthy individuals (mean age 35 + /-11, 77 female) were genotyped using Illumina genome-wide SNP chips. Cumulative polygenic risk for ADHD was computed for each individual based on summary statistics from the Demontis et al 2017 mega-analysis as implemented in PRSice-2 (Euesden et al, 2015). After abstaining from caffeine and nicotine for four hours, participants underwent positron emission tomography (PET) on a GE Advance scanner while at rest. For each subject, two sixty-second images of regional cerebral blood flow (rCBF) were collected after bolus intravenous injections of oxygen-15 water six minutes apart. A separately acquired T1-weighted structural MRI scan was used to guide spatial normalization of attenuation- and motion-corrected PET frames for use in voxel-wise analyses in SPM. Voxel-wise analysis was carried out with general linear modeling to test for effects of ADHD genetic risk, controlling for age, sex, and stratification effects. Results were corrected for multiple comparisons ($p < 0.05$, false discovery rate) within the striatum search space. Exploratory extrastriatal tests are reported at $p < 0.005$, uncorrected.

Results: Greater cumulative ADHD genetic risk was associated with greater striatal rCBF. A positive relationship between ADHD genetic risk and resting rCBF was also seen in clusters in the thalamus and prefrontal cortex.

Conclusions: These results in healthy individuals suggest that ADHD polygenic risk may be associated with resting state physiology in thalamo-striato-cortical circuitry previously implicated in the disorder, lending biological plausibility to the notion that cumulative common risk variation of small effect size may be meaningfully linked to illness pathophysiology and motivating further work to understand the specific molecular underpinnings of this phenotype.

Keywords: ADHD, Cerebral Blood Flow, Polygenic Risk Score

Disclosure: Nothing to disclose.

W157. Assessment of the Intravenous Abuse Potential of Serdexmethylphenidate, a Novel, Investigational Prodrug of d-methylphenidate: Evidence From Nonclinical and Clinical Studies

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Background: Serdexmethylphenidate (SDX) is a novel prodrug of d-methylphenidate (d-MPH) that has been incorporated into two investigational products (KP415 and KP484) for the treatment of attention-deficit hyperactivity disorder (ADHD). SDX was rationally designed to provide an extended duration of d-MPH exposure when taken orally as intended, but to release d-MPH less efficiently when administered via non-oral routes for the purposes of abuse. In single-dose, oral pharmacokinetic (PK) studies in humans, SDX was readily converted to active d-MPH, yielding appreciable exposure to d-MPH for a large proportion of the day. A series of studies was conducted to evaluate the performance of SDX with respect to receptor binding, in vitro metabolic stability, intravenous (IV) PK in rats, and IV PK and abuse potential in recreational stimulant abusers. SDX was compared to the positive control, d-MPH HCl, in rat and human studies.

Methods: Primary and secondary pharmacology: IC50 values of SDX (range: 0.03 to 10 μM) were determined using in vitro radioligand receptor binding assays for the dopamine (DAT), norepinephrine (NET), and serotonin (SERT) transporters, substrates associated with both the clinical efficacy and abuse-related effects of d-MPH. To detect potential adverse or unexpected activity, a panel of 68 molecular targets was evaluated using a concentration of 10 μM SDX. In vitro metabolic stability: The metabolic stability of SDX was evaluated in human whole blood, plasma, and human liver S9 fractions at a concentration of 10 μM. Triplicate samples were collected at various time points up to 90 min. Rat IV pharmacokinetics: Plasma PK parameters for d-MPH were generated after IV administration of SDX and d-MPH HCl, which were dosed at equimolar doses corresponding to 2.06 mg/kg of d-MPH content. Human abuse potential: Male and female recreational stimulant abusers who were able to distinguish a dose of IV d-MPH HCl (15 mg) from placebo were eligible to participate in the Treatment Phase. Thirty-one subjects were randomized to receive IV SDX (30 mg), IV d-MPH HCl (15 mg), and IV placebo in a double-blind, crossover fashion. The doses of SDX and d-MPH HCl were equivalent with respect to molar content of d-MPH. Serial PK samples, pharmacodynamic measures (e.g., Drug Liking, High and Take Drug Again visual analog scales [VAS]), and safety measures were collected up to 36 h after dosing.

Results: Primary and secondary pharmacology: IC50 values at the DAT, NET, and SERT were all > 10 μM, indicating no significant binding of SDX (intact prodrug) to these monoaminergic transporters. Similarly, in assays examining potential "off-site" pharmacology at an additional 68 molecular targets, no significant (< 50%) stimulation or inhibition of binding was observed. In vitro metabolic stability: In human whole blood and plasma, d-MPH was below the limit of quantitation at 0, 5, 10, and 20 min. following incubation with SDX, but was measurable at low levels (peak area ratios [PARs] of 0.2-0.4) at 45 and 90 min. In human liver S9 fractions, a small amount of d-MPH formed within 5 min. and increased slightly in a time-dependent manner up to a PAR of 5.2 at 90 min. Rat IV pharmacokinetics: IV administration of SDX resulted in significantly lower plasma concentrations of d-MPH when compared to d-MPH HCl. Mean peak exposure (Cmax) and exposure up to 2 h post-dose (AUC0-2h) for d-MPH released from SDX were approximately 12% and 17% of the respective values observed with d-MPH HCl. Human abuse potential: In recreational stimulant abusers, IV administration of SDX resulted in very little conversion to d-MPH over the 36-hr measurement period. Peak (Cmax) and overall (AUClast) d-MPH exposure were approximately 20.1% and 10.2% of the exposure observed with d-MPH HCl. Consistent with lower d-MPH exposure, the primary endpoint of mean Drug Liking Emax was significantly lower by more than a 10-point margin for SDX vs d-MPH HCl (53.8 vs 84.3, $p < 0.001$) and noninferior within an 11-point margin for SDX vs. placebo (56.6 vs. 53.8, $p = 0.001$). Similar results were observed for feeling High, where mean Emax was significantly lower for SDX vs. d-MPH HCl (14.5 vs. 77.4, $p < 0.001$), and not different from placebo (14.5 vs. 11.2, $p = 0.655$, where the null hypothesis was no difference between treatments). For the key secondary endpoint of Take Drug Again, mean Emax was significantly lower by more than a 10-point margin for SDX vs. d-MPH (19.6 vs. 63.3, $p < 0.001$), indicating that subjects were less willing to take SDX again. While there were small numerical differences in Take Drug Again Emax for SDX vs. placebo (19.6 vs. 14.4), SDX was not noninferior to placebo within an 11-point margin ($p = 0.275$). Adverse events typical of stimulants (e.g., euphoric mood, hypervigilance, palpitations) were more common during d-MPH HCl vs. SDX treatment.

Conclusions: These collective findings indicate that SDX, a prodrug of d-MPH, has no apparent affinity for a broad range of molecular targets and does not readily convert to active d-MPH in human blood, plasma, and liver S9 in vitro assays, or following IV administration in rats and humans. Furthermore, SDX produced a profile of pharmacodynamic effects that was statistically similar to placebo on multiple abuse-related endpoints. The performance of SDX following IV administration confirms the rational chemical

design of the prodrug and suggests that SDX, as a prodrug of d-MPH, is unlikely to be attractive for IV abuse.

Keywords: Abuse Potential, Methylphenidate, Prodrug, Attention Deficit Hyperactivity Disorder

Disclosure: KemPharm Inc., Consultant, Altreos Research Partners Inc., Employee

W158. Probing Neurocircuits: A Concurrent TMS-fMRI Investigation of State Dependence

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Background: A handful of preliminary studies of repetitive transcranial magnetic stimulation (rTMS) for neuropsychiatric disorders have suggested that therapeutic effects may be enhanced by modulating the state of the patient (Fryml et al., 2018; Isserles et al., 2013; Osuch et al., 2009). These studies have typically exposed the patient to clinically relevant cues (e.g., imaginal exposure in PTSD, craving in smoking) immediately prior and/or during rTMS. While these preliminary studies are promising, insights into the mechanism of action are limited. Transcranial magnetic stimulation delivered concurrent with functional magnetic resonance imaging (TMS-fMRI) extends conventional correlational imaging to causal neurocircuit mapping. That is, single pulses of TMS (spTMS) can be delivered to superficial cortical regions, and the activity in the connected networks mapped with the BOLD response. In the current study, we investigated whether state dependence, particularly pleasant and unpleasant emotional arousal, would influence the responsiveness to spTMS. We hypothesized that viewing emotionally arousing scenes would increase activation of the fronto-parietal network in response to spTMS targeted to left dorsolateral prefrontal cortex (dlPFC), and in the somato-motor network in response to spTMS targeted to primary motor cortex (M1).

Methods: Twenty-four individuals (11 females) free of physical or mental illness completed a picture-viewing paradigm in the MRI scanner. Pleasant, neutral and unpleasant pictures from the International Affective Picture System, as well as fixation crosses, were presented in 20-second blocks. Each block included eight pictures of the same valence, or a series of fixation crosses. While pictures were presented in the foreground, spTMS was delivered intermittently to left dlPFC or M1 in separate runs at 120% of motor threshold. Stimulation site and picture order were fully counterbalanced across participants. A Magstim figure-eight coil and Magstim SuperRapid stimulator were utilized for stimulation, in conjunction with a 12-channel RAPID Biomedical head coil. A T1-weighted anatomical volume was acquired using a Siemens Prisma 3 T Allegra MR scanner. Whole-brain fMRI data were collected with TR = 2.5. Data acquisition ceased at 2.4 s, allowing for the delivery of the TMS pulse prior to acquisition of the next volume. Functional time series underwent standard preprocessing with SPM12 (Friston et al., 2012).

Results: Whole-brain analysis demonstrated that TMS delivered to the dlPFC during emotional picture processing relative to fixation demonstrated reliably increased BOLD responses in bilateral fronto-parietal regions (i.e., left and right dlPFC and intraparietal sulci. TMS delivered to M1 during picture processing relative to fixation demonstrated reliably increased BOLD responses in pre-supplementary motor area and cerebellar regions of the somatomotor network. Reliably strong activation in visual cortex and amygdala were also evident in runs with TMS at both sites. This activation did not differ from that observed during emotional picture processing in the absence of spTMS, suggesting that concurrent TMS did not disrupt processing of the foreground task. Finally, no effects of pleasant versus unpleasant valence were observed for any contrasts. Instead a consistent emotional arousal effect was observed across contrasts.

Conclusions: Therapeutic rTMS is moving toward manipulating the cognitive/affective state of the patient during treatment delivery. This includes clinically relevant immersive environments, visual cues, and imaginal exposure. The current findings suggest that increasing emotional arousal during TMS, in fact, increases activation to TMS pulses in the distributed regions specific to the targeted network. Additionally, high arousing unpleasant and pleasant content similarly increased responses in the fronto-parietal and somatomotor networks. While the overall findings suggest that increasing emotional engagement during rTMS may be a productive means of strengthening the response within the targeted network, further investigation is warranted as to whether aversive clinical immersion is necessary to enhance rTMS efficacy. Immersion in pleasant contents could potentially be less burdensome and facilitate retention, while also engaging networks of interest.

Keywords: Interleaved TMS/fMRI, Emotion Modulation, Fronto-parietal, Somatomotor, State Dependence

Disclosure: Nothing to disclose.

W159. Targeting Functional Networks With Intracranial Stimulation to Enhance Working Memory in Humans

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Background: Working memory (WM) is an important component of cognition and is impaired in many psychiatric disorders such as schizophrenia and mood disorders. The neural substrates of WM are spread across many cortical regions and are coordinated by network oscillations. Periodic electrical or magnetic stimulation methods offer the ability to target these oscillations. In addition, effective engagement of oscillations may require spatial targeting of nodes of the network that coordinates WM. We hypothesized targeting regions that are functionally coupled through oscillations, at the frequency of the oscillation, would be effective in enhancing WM. To test this hypothesis, we performed direct cortical stimulation (DCS) in 3 participants when they performed a working memory task. Here we present results that demonstrate periodic stimulation synchronized across multiple regions is an effective strategy in improving cognition.

Methods: All procedures involving human participants were approved by the Institutional Review Board of UNC-CH and informed consent was obtained. The participants were recruited by invitation from the patients who were undergoing invasive monitoring for surgical resection of seizure focus. Two of the participants (P2, P3) were implanted with stereo electroencephalography (sEEG) electrodes while one (P1) was implanted with subdural strip electrodes covering frontal, temporal and parietal regions, the locations being completely dictated by clinical needs. Participants performed a classical Sternberg WM task in a baseline session while intracranial EEG (iEEG) was collected concurrently using Netstation 410 (Electrical Geodesics Inc, Eugene, OR). Functional networks were identified from this baseline data using weighted phase lag index (wPLI). Two electrode pairs that showed peaks in the wPLI spectrum in the alpha and theta frequency bands were chosen as stimulation electrodes.

In a second session, the participants performed the WM task again during which stimulation was applied in-phase, i.e.,

stimulation was applied simultaneously between the two electrode pairs time-locked to trial start. Stimulation consisted of a train of biphasic electrical pulses 2 mA in amplitude and frequency matched to the frequency observed in wPLI spectrum. Control conditions included sham in which no stimulation was applied and anti-phase condition, in which stimulation applied between one pair of electrodes was temporally offset from the other by half the inter-pulse-interval of the pulse train. The three conditions were randomly inter-leaved across the trials of the task. The stimulation was delivered using Cerestim M96 cortical stimulator (Blackrock microsystems, Salt Lake City, Utah).

Results: In-phase stimulation resulted in an increase in accuracy compared to sham across three participants (In Phase: 84.72 ± 8.00 vs Sham 70.31 ± 7.69 (mean ± sd), $p = 0.02$; chi-squared test of independence). While in-phase stimulation resulted in increased accuracy compared to anti-phase stimulation in 2 of the 3 participants, statistical significance was not achieved (In Phase: 84.72 ± 8.00 vs Anti 75.56 ± 12.62 (mean ± sd), $p = 0.20$; chi-squared test of independence). Reaction time analysis did not reveal any significant difference between the three conditions ($p = 0.70$; linear mixed effects model with random factor participant and fixed factor condition).

We employed an independent component analysis (ICA) approach to remove stimulation artifacts from the iEEG data. Following this, functional connections that were strongest during baseline session (excluding functional connections from/to the stimulation electrodes) were analyzed for effects of stimulation. In-phase stimulation enhanced functional connectivity relative to sham and anti-phase stimulation in only one participant (P2, difference between in-phase and sham: 0.11 ± 0.11 (mean ± sd), $p < 0.01$; one sample t-test with Bonferroni correction, difference between in-phase and anti-phase: 0.10 ± 0.10, $p < 0.01$) while anti-phase stimulation enhanced functional connectivity relative to sham in one participant (P3, difference between anti-phase and sham: 0.02 ± 0.07, $p = 0.01$ one sample t-test with Bonferroni correction). The variability in observed differences can be attributed to the heterogeneity in electrode locations from which functional networks during stimulation were computed.

Conclusions: The results demonstrate that multi-site stimulation is effective in enhancing cognition. Specifically, in-phase stimulation of regions chosen by endogenous functional coupling, at a frequency matched to the frequency of functional coupling was determined to improve accuracy in a working memory task. The results imply functional connectivity may be a suitable marker of stimulation targets in contrast to spectral power modulation. With the increasing interest in implanted devices for treating psychiatric disorders, the study provides feasibility of using implanted devices for improving cognitive symptoms by targeting networks.

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Keywords: Brain Stimulation, Working Memory, Large Scale Networks

Disclosure: Pulvinar Neuro LLC, Consultant, Pulvinar Neuro LLC, Stock / Equity

W160. A Case Series on Deep Brain Stimulation of the Medial Forebrain Bundle in OCD: Rapid Improvement of OCD Symptoms and Antidepressant Response

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Background: Deep brain stimulation (DBS) to nucleus accumbens, ventral capsule, ventral striatum, subthalamic nucleus and inferior thalamic peduncle have been proposed as possible treatment for severe, treatment resistant obsessive-compulsive disorder (OCD). 60% of patients treated with DBS to one of these regions responded to treatment and overall symptom reduction was 45.1% measured by Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Alonso et al., 2015). We reported notable treatment effects (35 and 50% YBOCS reduction after 1 year) in two patients with treatment resistant OCD who received DBS to another target region, the medial forebrain bundle (slMFB). Up to now, rapid and sustained (up to 4 years) antidepressant effects of slMFB DBS have been observed for treatment-resistant depression. Under the assumption of a dysfunction of the reward system in depression, these effects can be explained by the slMFB's crucial role in the reward system. As the slMFB is also a structure connecting relevant target regions in OCD treatment, it therefore seems to be a suitable DBS target for this disorder itself.

Methods: Four patients (1 f, 3 m) suffering from severe, treatment-resistant OCD have been treated with DBS to the slMFB (electrodes: DB2202-Directional, BostonScientific; three with a rechargeable, one with a non-rechargeable pulse generator) following the protocol described in Coenen et al. (2017). Patients were between 30 and 50 years old. All patients received cognitive psychotherapy with exposure, inpatient and outpatient treatments and various medications administered at adequate dosages and for adequate durations before DBS. None of these treatments had substantial lasting effects on OCD symptoms. One patient (#4) had been treated with DBS to the VC/VS for the last 9 years, but while compulsive behaviors had been slightly reduced, obsessive thoughts remained unchanged.

Implantations and stimulation onset took place between December 2017 and March 2018. OCD symptoms (via Y-BOCS) and depressive symptoms (via Montgomery Åsberg Depression Rating Scale, MADRS) were measured at two preoperative visits and about monthly after stimulation onset. Bilateral stimulation has been performed continuously and stimulation parameters have been adjusted individually in various titration visits. Frequency and pulse width kept unchanged at 130 Hz and 60µs. Minimal/maximal current applied to the slMFB was 2.0 mA/ 3.1 mA.

As this is a case series, treatment was neither blinded nor controlled.

Results: Compared to baseline, three patients experienced rapid and remarkable reduction of symptoms in Y-BOCS after stimulation onset. Mean Y-BOCS score of two preoperative visits for each patient was 43.5 (patient #1), 41 (#2), 21.5 (#3) and 32 (#4). After one month of stimulation the score dropped to 24 (#1), 18 (#2) and 9 (#3) while it kept clinically stable for patient #4 (Y-BOCS score 27), leading to a mean reduction of 43,67% (SD = 16,97). After two months reduction increased to 49,65% (SD = 33,35) compared to baseline with still no relevant improvement for patient #4 (Y-BOCS score 29). Three to five-month data from the three responding patients show a stable effect. Patient #4 showed a noticeable improvement after four months of stimulation (Y-BOCS score 12). The stability of this effect remains unclear as further data is not yet available.

In all patients a reduction of depressive symptoms was observed. Mean reduction rate of MADRS-score was 72.46% (SD = 32.08) after two months of stimulation compared to baseline. This rate was even higher in the three patients (#1-3) that showed a decline of OCD symptoms (reduction rate 90.61%, SD = 7.44) and remained stable in the following visits. Patient #4 experienced a slower but steady reduction of depressive symptoms. His MADRS score had dropped from 30.5 (mean of two preoperative visits) to 25 at the two-month visit. Along with the reduction of OCD symptoms in month four, he showed substantially less depressive symptoms (MADRS score 12) and reported a considerable increase of quality of life.

Related adverse events were reported only during parameter adjustment in form of accommodation problems or diplopia and disappeared immediately after parameter adjustment.

Conclusions: These results support the proposal of the slMFB as target region for DBS in OCD treatment. Applying a 35% reduction in Y-BOCS as response cut off like in Alonso et al. (2015), patients #1-3 reached response after one month of stimulation, #4 after four months. Therefore, the reduction of symptoms could be observed rapidly as already seen in depression.

As we would expect in the light of the results of slMFB stimulation in depression, depressive symptoms declined as well. As OCD and depressive symptoms seem to decline simultaneously the above-mentioned suggestion of a shared relevant disease network is encouraged.

The patient who did not respond immediately had been treated with DBS to the VC/VS for the last 9 years and therefore differs from the other patients. It remains unclear, why he showed a delayed response. To generate more insight into the mechanism of action of this treatment on a metabolic level, PET-studies might be useful.

As promising as these results appear, this is a small, uncontrolled, unblinded case series and results should not be overestimated. Controlled, randomized longterm studies that systematically examine patients and their potential response throughout treatment are therefore necessary.

Keywords: Deep Brain Stimulation, Obsessive-Compulsive Disorder (OCD), Medial Forebrain Bundle

Disclosure: Nothing to disclose.

W161. The Role of Placebo Response in the Outcomes of Clinical Trials for Neuropsychiatric and Medical Conditions

Abstract not included.

W162. Double Dissociation of Nicotinic Alpha-7 and Alpha-4/Beta-2 Subreceptor Agonists for Enhancing Learning and Attentional Filtering of Distraction

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Background: Nicotinic acetylcholine receptors (nAChR) modulate attention, memory, and higher executive functioning, but it has remained unclear whether nAChR sub-receptors tap into different neural mechanisms of these functions. To understand whether nACHR sub-receptor actions have unique contributions to attention versus memory it will be pivotal to quantify their influence on these functions in an experimental paradigm that (1) uses a task that quantifies both functions, and (2) optimizes the dose for each sub-receptor agent independently for the task. In addition, to infer the neural mechanisms of sub-receptor specific functioning it will be critical to show their unique functional contributions in an animal model that uses similar brain systems and behavioral strategies to solve attention and learning tasks. There are only few studies that fulfill these criteria, leaving open whether nAChR sub-receptor drug actions affects different brain mechanisms during attentional focusing and during learning to adapt to environmental demands.

Methods: We set out to contrast the contributions of selective alpha-7 nAChR and alpha-4/beta-2 nAChR agonists in mediating value learning and attentional filtering of distractors in the nonhuman primate using two approaches. In a first phase we provide a comprehensive meta-survey of available behavioral studies testing the behavioral effects of either alpha-7 nAChR or alpha-4/beta-2 nAChR agonists in the nonhuman primate. In a second phase, we selected an alpha-7 nAChR and an alpha-4/beta-2 nAChR agonist to test their influence on a feature-based learning task with varying attention demands. In two macaque monkeys, we tested varying doses of systemically applied drugs on various behavioral indices from that feature-based learning task.

Results: We found that the alpha-7 nAChR agonist PHA-543613 selectively enhanced the learning speed of feature values but did not modulate how salient distracting information was filtered from ongoing choice processes. In contrast, the selective alpha-4/beta-2 nAChR agonist ABT-089 did not affect learning speed but reduced distractibility. This double dissociation was dose-dependent and evident in the absence of systematic changes in overall performance, reward intake, motivation to perform the task, perseveration tendencies, or reaction times.

Conclusions: These results suggest nicotinic sub-receptor-specific mechanisms consistent with (1) alpha-4/beta-2 nAChR specific amplification of cholinergic transients in prefrontal cortex linked to enhanced cue detection in light of interferences, and (2) alpha-7 nAChR specific activation prolonging cholinergic transients, which could facilitate subjects to follow-through with newly established attentional strategies when outcome contingencies change. These insights will be critical for developing function-specific drugs alleviating attention and learning deficits in neuropsychiatric diseases.

Keywords: Alpha-7 Nicotinic Acetylcholine Receptor, Nicotinic Acetylcholine Receptors, Attention, Brain, Dopmaine, Adaptive Behavior, Learning, Memory

Disclosure: Nothing to disclose.

W163. Acute Nicotine Abstinence Decreases Event-Related Potential Correlates of Post-Error Processing but not Conflict Resolution

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Background: Errors committed during behavioral tasks result in an event-related potential (ERP) termed the error-related negativity (ERN) reflecting post-error cognitive processing. The anterior cingulate cortex (ACC) is a neural generator of the ERN and implicated in dysregulated circuits related to addiction. The Go/NoGo (response inhibition) and Flanker (response conflict) tasks are commonly used to elicit an ERN. The former requires the participant to override a prepotent response mapped to frequent Go stimuli by inhibiting responses to less frequent NoGo stimuli, thereby eliciting few commission errors. The latter requires the participant to respond to every stimulus, conflating response inhibition and conflict resolution, thereby eliciting increased commission errors relative to the Go/NoGo task. Neural correlates

of post-error processing differ as a function of drug dependence and can predict addiction treatment outcomes, suggesting a potential biomarker. However, the relationship between error-processing and pharmacological state (e.g., acute withdrawal) and trait (i.e., dependence severity) is unclear. For smokers, the first few hours of a quit attempt are often the most difficult, which may be reflected in cognitive processing of response errors. We hypothesized that smokers in acute abstinence, relative to a nicotine sated condition, would exhibit state-dependent neural deficits in post-error processing reflected in smaller ERN amplitudes in both Go/NoGo and Flanker tasks.

Methods: Individuals with (N = 24) and without (N = 20) nicotine dependence completed a Go/NoGo and a Flanker task while ERPs were recorded simultaneously with BOLD acquisition in a Siemens Allegra 3 T scanner (EEG data only presented herein). On two separate days, participants were instructed to refrain from cigarette smoking for 12-hours prior to EEG recording and wore either a placebo or nicotine patch in a blinded, counterbalanced order. A 64-channel MRI-compatible Brain Vision system was used to collect EEG data. Brain Vision Analyzer software was used to remove MRI gradient, cardioballistic, eye, and movement artifacts from the EEG data. Mean amplitudes within the ERN window, -25 to 75 ms relative to a commission error, were calculated in twelve electrodes for analyses: F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, and CP4. A three-way interaction between TASK (Go/NoGo vs Flanker), GROUP (smoker vs control), and PATCH (placebo vs. nicotine) in the response-locked ERN window was tested in a mixed-model analysis to assess neural correlates of post-error processing.

Results: The three-way interaction of TASK X GROUP X PATCH was significant in the ERN window, $F(1,918.29) = 8.35$, $p = .004$. Also, the TASK X PATCH, $F(1,918.29) = 4.25$, $p = .04$, and GROUP X PATCH, $F(1,37.93) = 4.12$, $p = .05$, interactions were significant. Simple effects indicated that the smoker group exhibited a reduction in ERN amplitude (i.e., less negative) on the placebo (abstinent) relative to nicotine patch (sated) condition, in the Go/NoGo but not in the Flanker task. No behavioral differences were noted on either task.

Conclusions: ERN amplitude, reflecting post-error processing, elicited during the Go/NoGo response inhibition task was reduced in smokers in an abstinent relative to nicotine replacement sated state. ERNs in nonsmokers were not modulated by either patch manipulation or task. There were no differences in task performance as a function of group or pharmacological state manipulation. In contrast, the ERN amplitude elicited during the Flanker response conflict task did not differ as a function of either group or drug manipulation. Therefore, post-error processing appears to be compromised in acutely abstinent smokers; however, when the combination of post-error processing and conflict monitoring is assessed, both processes remain intact Assessing acute state of the smoker may be important in considering ERNs elicited during a response inhibition task as a biomarker of ability to maintain long-term abstinence. These state-dependent results contribute to a growing body of evidence suggesting pharmacological state should be considered when assessing neural correlates of addiction. Thus, understanding state-dependent modulations, specifically acute abstinence, may help identify biomarkers useful for developing individualized addiction interventions and decrease risk for relapse.

Supported by NIDA-IRP

Keywords: Nicotine Addiction, ERP, Error Processing

Disclosure: Nothing to disclose.

W164. Gender Balance in Neuropsychopharmacology (NPP) Function: Data Analyses and Dissemination via Social Media

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Background: Gender balance is an important issue for Neuropsychopharmacology (NPP) and the American College of Neuropsychopharmacology (ACNP), the organization which NPP represents. There is increasing awareness of the representation of men and women in science faculty, academic organizations, and publication and editorial processes; however, gender balance in NPP function has not been previously explored in any depth. To begin addressing this issue, we undertook a data-driven approach to characterize representation of men and women in journal function (processes in which editors, reviewers, and authors are engaged). Our foremost goal is to identify and address areas of imbalance with interventions to improve inclusivity while maximizing equitability.

Methods: Detailed data sets reflecting reviewer demographics for NPP manuscripts became available starting in 2011, so this served as our earliest time point for analysis. For comparisons of editorial and reviewer roles, reviewer metrics, and corresponding authorship of accepted papers, we examined 2011-2017. Assessment of author suggestions for peer reviewers required prospective data collection that was enacted on January 1, 2018, enabling only a partial year analysis. Detailed on-line searches for the use of gender-specific pronouns on websites and/or photographs were made to match an individual's indicated (first) name to their gender, although some inaccuracies using this method are possible despite our best efforts. To estimate the impact of social media in promoting awareness of gender balance in journal function, we examined key metrics from nine Tweets derived from the NPP Editors' Twitter account (@NPP_Journal) that specifically related to gender balance, including highlights of an all-women authored paper, two gender-specific studies, funding opportunities for women scientists, additions to the editorial board, and release of data derived from this project.

Results: In 2018, 43% of Senior Editors are women (6/14), whereas in 2011, 25% (3/12) were women. Among the Editorial Board, in 2018 33% of Editorial Board Members (17/51) are women, while in 2011, by comparison, 12.5% (6/48) were women. Regarding reviewers, by the end of 2017 the total number of women serving as reviewers and the total number of reviews completed by women were 34% and 33%, respectively, compared to 30% and 29% in 2011. While there are more men in the reviewer pool, the average number of invitations to review, acceptances to review, declines to review, and the number of reviews completed, showed balance and stability over time, with no statistically significant gender differences. Although women tend to take longer to review and submit fewer reviews on time, these differences were small in effect size (Cohen's $d = 0.04$-0.18). Of the 583 manuscripts submitted to NPP between January 1 - June 30, 2018, 38% of corresponding authors were women. Congruent with this percentage, in 2017 (the most recent full year for which all manuscript decisions have been rendered), 39% of accepted papers had women as corresponding authors, improving nominally from 34% in 2011. In 2018, both men and women more frequently suggested (and excluded) reviewers who are men (P's < 0.01), although women corresponding authors were more likely to suggest women as reviewers ($P < 0.01$). The nine Tweets by NPP Editors specifically related to gender balance reached 104,616 Twitter feeds in total (11,624 on average), with a total 4,329 specific interactions (481 on average; including likes, retweets, comments, link clicks and reads), indicative of the wide influence social media

has in stimulating awareness of gender balance in journal function.

Conclusions: Many NPP metrics are encouraging, especially when viewed over time, but there are areas where improvements are needed. The representation of women in editorial, reviewer, and corresponding author roles largely align with the estimate (39%) of women faculty in neuroscience [https://biaswatchneuro.com/baserates/neuroscience-base-rates]. However, because author suggestions are frequently considered in the review process, gender imbalance within suggested reviewers could be a contributor to gender imbalance in reviewer demographics, leading to imbalance in representation on the Editorial Board. Going forward, we have taken three explicit steps to improve reviewer balance, including 1) written reminders to Senior Editors, 2) detailed instructions in the on-line submission platform to encourage authors to be mindful of the suggestions they make, and 3) dissemination of data gleaned from this gender balance assessment on social media accounts to broadly promote awareness and stimulate discussion among the readership. We plan to continue to collect data on author suggestions for the period of July 1-December 31, 2018, to determine if these initial interventions are effective in improving the balance in suggested reviewers. We want to minimize creation of burdens on faculty from groups that are underrepresented in NPP-related disciplines but recognize that optimizing balance is a critical element of NPP realizing the goal of equitability in the publication process. We acknowledge that gender is only one demographic of which we need to be more mindful when considering balance in journal function, and planning is underway to examine additional demographics in future studies. Ultimately, solutions will require teamwork and cooperation from our entire community.

Keywords: Sex Differences, Neuropsychopharmacology, Journal Function

Disclosure: Nothing to disclose.

W165. Aberrant Causal Reasoning in Obsessive-Compulsive Disorder

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Background: Individuals with Obsessive-Compulsive Disorder (OCD) engage in maladaptive repetitive behaviors reflecting erroneous causal beliefs about the environment. Large knowledge gaps remain regarding causal reasoning deficits in OCD, and the neurobiology of this core clinical abnormality remains unclear. Causal reasoning is a complex construct relying on several distinct underlying computations, including the ability to learn contingencies (specific contingency learning; SCL) and to represent abstract outcomes (outcome representation; OR). These computations are difficult to dissociate in real-world situations using existing neurocognitive assessments. The neural substrate most consistently implicated in both OCD pathology and causal reasoning is the orbitofrontal cortex (OFC). However, the specific role that OFC dysfunction plays in OCD symptoms remains unknown.

Methods: We have developed a neurobiologically-informed behavioral paradigm designed to disambiguate the specific elements of causal reasoning. Specifically, our task assesses the hypothesized computations of lOFC and mOFC (SCL and OR, respectively) in patients with OCD and matched controls. The paradigm is optimized in conjunction with state-of-the-art neuroimaging to test the hypothesis that behavioral and neural signals of specific contingency learning versus outcome representation differ in OCD relative to matched controls. In turn, we will quantify relationships between symptoms (dimensionally assessed through a battery of well-validated clinical measures), neural signals, and behavioral measure of specific contingency learning and outcome representation. We will collect data in a sample of 48 patients and 48 matched control subjects. We hypothesize that patients will exhibit abnormalities in SCL and decreased activation of lOFC during SCL, and that OR and corresponding mOFC activation will be comparable to controls.

Results: Preliminary behavioral data from 8 patients with OCD and 5 healthy controls show feasibility for the task and support our hypothesis that SCL is specifically impaired in OCD, while OR is intact. The finding that SCL is impaired in OCD was demonstrated across five separate analyses in the preliminary sample. Preliminary neuroimaging data ($n = 3$) on Yale 3 T Prisma scanner using Human Connectome Project (HCP) protocols demonstrate lOFC activation (amongst a broader set of regions) in a contrast assessing activation during SCL; this is consistent with our predictions and with recent findings implicating lOFC in SCL. This highlights the power of the proposed analytic pipeline to produce high quality results even from $n = 3$, supporting the feasibility of the proposed paradigm, acquisition and analysis methods. Behavioral and neuroimaging data collection are ongoing.

Conclusions: This work represents the first focused examination of discrete component processes of causal learning in OCD. Innovations include a theoretically-grounded focus on causal learning and its subcomponents, a novel, feasible, and well-validated behavioral task that dissociates these subcomponents, and state-of-the-art HCP imaging methodology that has not previously been deployed in studies of OCD. Confirmation that SCL and corresponding lOFC recruitment is specifically deficient in OCD and correlates with symptomatology would represent a major theoretical advance and would provide the foundation for the future development of novel, targeted therapeutic strategies.

Keywords: Obsessive Compulsive Disorder, Neurocognition, Causal Reasoning, Orbitofrontal Cortex (OFC)

Disclosure: Nothing to disclose.

W166. Semantic Relationships of Obsessions: Novel Insights Into Clustering and Frequencies of Symptom Subtypes in Obsessive-Compulsive Disorder From a Large International Mobile Application Dataset

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Background: Obsessive-compulsive disorder (OCD) is a common psychiatric disorder with an estimated lifetime prevalence of approximately 2%, characterized by recurring thoughts, urges, or images (obsessions) that trigger anxiety and distress, and rituals or behaviors (compulsions) that temporarily decrease distress, but reinforce obsessions over time. Symptoms of OCD can manifest in a variety of seemingly disparate ways. Symptom category-based factor analytic studies demonstrate convergence on three dimensions of obsessions (excluding hoarding): contamination, aggressive/sexual/religious/somatic ("harm") obsessions, and symmetry/order obsessions. Studies using individual item-based rather than pre-defined category-based symptoms tend to converge on five categories: contamination, aggressive/sexual/religious, symmetry/order, aggressive, and somatic obsessions. Cluster analyses have also been applied to identify subgroups of

OCD symptoms. The majority of these approaches, however, have relied on participant selection from pre-defined sets of obsessions and compulsions - most commonly the Yale-Brown Obsessive-Compulsive Scale symptom checklist. However, this may introduce bias as it could lead to participants "fitting" their experience into the terms on the checklist. Using free-entry terms that are spontaneously generated by participants could reduce this bias. Although more difficult to classify, the semantic relationships of freely-entered words representing obsessions can be analyzed for their clustering relationships in the English language, e.g., using natural language processing approaches, which in term could provide a better understanding of semantic themes.

To apply this approach, we obtained free-entry data on obsessions from a mobile health treatment platform developed by nOCD (www.treatmyocd.com) to provide users with customizable exposure and response prevention (a form of cognitive-behavioral therapy for OCD) to overcome the barriers associated with lack of accessible treatment for OCD. The goal was to apply natural language processing using semantic clustering to understand thematic relationships of obsessions in OCD and to compare relative frequencies of these themes.

Methods: The mobile application, nOCD, includes two features where users who self-identify as having OCD can input their current obsession(s): the SOS feature and the hierarchy, which they then can use for planned exposure exercises. Obsessions that had been inputted by users were assigned an anonymous user identification number, and all data were de-identified.

Entries were first parsed into single words. Single words were assigned a frequency as to how often they occurred across all individuals' entries and then sorted by the frequency of occurrence. Two psychiatrists (AL and JF) chose the top 25 OCD-relevant words. Words that were not in agreement were decided upon by a third clinician with OCD experience, to reach a final consensus of 25 words. Semantic vector space modeling was applied using Global Vectors for Word Representation algorithm (GloVe), an unsupervised learning algorithm for obtaining vector representations for words. We used pre-trained GloVe word embedding vectors based on global word-word co-occurrence statistics from a 6-billion-word corpus. Resulting representations depict linear substructures of the word vector n-dimensional space. We chose 100 dimensions for this exploratory analysis.

Results: We obtained 6453 words representing obsessions from 4073 individuals of age 17 and older, self-identified as having OCD, across 90 countries. Using previously defined canonical OCD factor structures, we found that 1242 words related to harm, 749 related to contamination, and 122 related to symmetry/order (or, "not just right experiences"). Harm obsessions were significantly more frequent than contamination or symmetry/order (Chi-sq(2) $= 579.6$, $p < .00001$). The clustering algorithm produced a topological pattern demonstrating a large but diffuse central cluster of harm-themed words, continuous with one dimensional arm extending from this towards a sexual/homosexual/relationship theme and another extending from this main "harm" cluster towards a contamination theme.

Conclusions: In this large, international dataset we applied a relatively unbiased approach to understanding frequencies and themes of obsessional thoughts reported in self-identified individuals with OCD. Results suggest that obsessions with the theme of harm are by far the most frequently occurring. Moreover, the theme of harm may semantically link the majority of obsessions, with some divergence for contamination and sexual/homosexual/relationship themes.

Keywords: Obsessive-Compulsive Disorder (OCD), Obsession, Clinical Subtypes, Semantic, Word Embedding Clustering

Disclosure: nOCD, Inc., Consultant, Self

W167. Amygdala Ablation: A Neurosurgical Approach to PTSD Treatment?

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Background: Posttraumatic stress disorder (PTSD) is a severe psychiatric response to a traumatic event with a prevalence of 5-10% in the general population. About 30-50% of patients are refractory to current therapies, making PTSD a chronic, debilitating disorder with significant emotional and financial burden to individuals and society. Neurobiological research has consistently indicated increased reactivity of the amygdala in PTSD. Moreover, amygdala hyper-reactivity predicts development and maintenance of PTSD symptoms and treatment non-response [1], suggesting that the amygdala could be a target for therapy. Notably, brain injury inclusive of the amygdala is protective against developing PTSD [1], and a case report suggests improved PTSD symptoms after unilateral temporal lobectomy for epilepsy [2]. The highly invasive nature of neurosurgery and prolonged neurocognitive impact of temporal lobectomy have previously confounded investigation of the impact of this surgical intervention upon PTSD. Highly-selective stereotactic laser amygdalohippocampotomy for epilepsy, however, has recently emerged as a minimally invasive alternative to open surgery that reduces collateral injury and provides superior neurocognitive outcomes. Notably, patients with PTSD are more likely to develop epilepsy, but the extent of comorbid epilepsy and PTSD has been historically under-recognized. The objectives of the study were: 1) examine rates of comorbid PTSD and epilepsy in a large inner-city population; 2) complete multimodal assessments of patients undergoing unilateral amygdala ablation for epilepsy as a unique opportunity to prospectively investigate the effects upon comorbid PTSD without otherwise altering clinical care.

Methods: For the first research question, data was analyzed from the Grady Trauma Project - a large study assessing PTSD in a highly traumatized, low socio-economic status, minority urban population. PTSD symptoms were assessed with the PTSD symptom scale and a self-report measure was used to track the diagnosis of epilepsy and/or history of experiencing seizures. Data for both measures were available for $n = 2677$ (89% female). For the second research question, patients with medial temporal lobe epilepsy (MTLE) with or without comorbid PTSD and who undergo stereotactic laser ablation of the amygdala for medically refractory epilepsy were recruited from the Emory epilepsy surgery program. Four MTLE patients (3 female), 2 of which (both female) met DSM-5 criteria for PTSD, completed preoperative evaluation and underwent laser ablations encompassing unilateral amygdala. Preoperative and postoperative assessments included (1) PTSD symptoms by a licensed clinical psychologist using the clinician-administered PTSD scale; (2) fear-potentiated startle during a fear conditioning and extinction paradigm; (3) emotional memory encoding; and (4) structural and functional MRI data (3 T Siemens Trio) during viewing of fearful and neutral faces.

Results: Of the $n = 2677$, 194 subjects (7.2%) reported epilepsy or seizures. 47% of the epilepsy/seizure patients met DSM-IV criteria for PTSD compared to 34% in the non-epilepsy/seizure controls. Chi-square tests indicated that these proportions were significantly different between the groups ($\chi 2 = 13.91$, $p < 0.001$). The study of amygdala ablation in patients with MTLE + /- PTSD is ongoing. One MTLE + PTSD patient who underwent laser ablation of right amygdala and hippocampus completed pre- and post-operative evaluation at 6 months while post-operative evaluations of the 3 remaining patients are pending. At 6 months, the patient experienced no further epileptic seizures, and had a > 30%

reduction in PTSD symptoms (CAPS score decrease from 32 to 22), suggesting a clinically significant improvement. On the fear-potentiated startle task, she showed improved discrimination between danger and safety cues from -23% pre-ablation to 72% post-ablation. Her emotional memory showed an increase in remembered items from 25% pre-ablation to 36% post-ablation. Region of interest functional MRI analyses showed an increase in activation in the rostral and dorsal anterior cingulate cortex of 21% and 14%, respectively, from pre- to post-ablation during the presentation of fearful versus neutral faces.

Conclusions: The under-appreciated comorbidity between PTSD and epilepsy suggests a possible pathophysiological link mediated by the amygdala and highlights the therapeutic feasibility of unilateral minimally-invasive neurosurgical amygdalotomy. To our knowledge, this is the first prospective investigation of the effect of unilateral amygdala ablation on PTSD symptoms and neurobiology. The first case showed significant post-ablation improvements in clinical measures and biomarkers of PTSD, including psychophysiological measures of fear conditioning and extinction, emotional memory, and neural correlates of fear processing and frontal inhibition. The results provide a basis for investigating the extent of dominant versus nondominant medial temporal structures that must be ablated to confer benefit for PTSD. Our larger ongoing study will provide insights into patient selection, neurocognitive impact, and long-term effectiveness of amygdalotomy as a novel neurosurgical therapy for chronic medically-refractory PTSD.

Keywords: PTSD, Epilepsy, Amygdala Ablation, Psychophysiology, Functional and Structural MRI

Disclosure: Nothing to disclose.

References:

1.Koenigs, M., et al., Nature neuroscience, 2008. 11(2): p. 232-237.

2.Basheikh, M., Epilepsy Behav Case Rep, 2017. 20(8): p. 14-17.

W168. Kappa Opioid Receptors Drive the Tonic Aversive Component of Chronic Pain

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Background: Chronic pain is second only to bipolar disorder as the major cause of suicide among all medical illnesses. Co-occurring psychopathology in chronic pain patients significantly impacts pain perception (heightened pain intensity), increases pain-related disability, decreases response to treatment and increases risk of prescription opioid misuse. In humans, kappa opioid receptor (KOR) activation causes anxiety, discomfort, agitation, depression and dysphoria. Considering that the circuitry involved in pain processing and affective/motivational systems overlaps extensively, we asked whether KOR contributes to the aversive nature of chronic pain.

Methods: We have used a combination of biochemical, molecular and in vivo techniques. Such techniques include cRNA scope fluorescent multiplex in situ hybridization, in situ GTPgS autoradiography, in vivo microdialysis, conditioned place aversion and preference, von frey testing, western blotting and conditional knockout animals. N = 6-20 and data are presented as raw data with 25 and 75% quartiles.

Results: In a rodent model of chronic neuropathic pain, we show that the endogenous tone of the KOR system within mesolimbic dopaminergic circuitry is increased. Importantly, we show that KOR blockade or elimination of KOR in midbrain dopamine neurons alleviates the tonic-aversive component of chronic neuropathic and inflammatory pain in male, but not female mice. KOR blockade also alleviates depressive and anxiogenic effects associated with neuropathic pain but this effect is not sex-dependent, suggesting a diversion of mechanisms between affective dimensions of chronic pain and the on-going tonic-aversive state.

Conclusions: Our results strongly support the use of KOR antagonists as therapeutic treatments to alleviate the emotional, tonic-aversive component of chronic pain, which is argued to be the most significant component of the pain experience that impacts a patient's quality of life.

Keywords: Kappa Opioid Receptor Antagonist, Dopamine, Pain, Reward and Aversion

Disclosure: Nothing to disclose.

W169. A Model Psychopharmacology Curriculum for Teachers of Psychiatric Residents

Abstract not included.

W170. Trauma Potentiated Startle and Cortisol Reactivity as Psychophysiological Mechanisms of Treatment Response Within Prolonged Exposure Therapy for Post-traumatic Stress Disorder

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Background: While exposure-based psychotherapy is recommended as a first-line treatment for PTSD given strong evidence for its effectiveness, some fail to receive full benefit. Prolonged exposure (PE) demonstrates large treatment effect sizes in randomized trials, however approximately one-third to one-half of patients do not demonstrate clinically meaningful symptom change (Steenkamp, Litz, Hoge, Marmar, 2015). Identification of clinical features that robustly and reliably explain variability in treatment response has proven difficult. Previous research suggests that pre-treatment psychophysiological markers are associated with PE treatment response (e.g., Robison-Andrew et al 2014; Norrholm et al 2016) in traditional outpatient PE. Psychophysiological data may be important sources of data for investigating variability in treatment response and changes over the course of treatment. Understanding biological mechanisms of treatment response can help elucidate why some individuals fail to receive full benefit and inform efforts to improve treatment efficacy and may be used to inform personalized medicine.

Methods: Participants in the present study (N = 50; data collection is ongoing with 15-20 enrollments per month) included veterans or military service members with primary PTSD diagnosis who received a two-week intensive PE treatment. Psychophysiological paradigms provide strong translational laboratory models for investigating fear based responding in PTSD. Participants underwent a psychophysiological assessment procedure at pre and post-treatment that included trauma-potentiated startle. Startle response was assessed while participants viewed three virtual reality (VR) trauma-relevant scenes presented through a head mounted display for 15 minutes. Salivary cortisol was also collected immediately prior to, after, and 15 minutes after VR trauma prime. The focus of the present investigation was to investigate the change in trauma-potentiated startle and salivary cortisol from pre to post treatment, and to investigate if changes differed for high treatment responders versus low treatment responders.

Results: Results indicate that 29.6% were classified as high treatment responders, as defined by a 50% or greater reduction in

PCL-5 symptoms from baseline. Patients demonstrated a reduction in cortisol reactivity at post-treatment compared to pre-treatment, $t = 2.53$, $p = .015$. Trauma potentiated startle was observed in all patients regardless of responder status, in that startle magnitude was increased during VR stimuli relative to baseline, $F = 13.31$, $p = 0.001$. However, in high treatment responders, there was an interaction of VR with time, $F = 10.18$, $p = 0.004$, in that VR scenes did not potentiate startle post-treatment. That is, high treatment responders were less reactive to trauma stimuli following PE treatment. There was no effect of time in the low responder group, indicating that their reactivity to trauma stimuli didn't change following treatment.

Conclusions: These results suggest that trauma-potentiated startle may represent an objective marker of fear- and anxiety-related symptom reduction that is sensitive to both short- and long-term treatment approaches. This finding can help inform potential treatment augmentation efforts aimed at patients who fail to receive full benefit.

Keywords: PTSD, Exposure Therapy, Psychophysiology

Disclosure: Nothing to disclose.

W171. A Unified and Generalizable Model for Online Latent-State Learning

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Background: Significant effort in computational psychiatry is devoted to the quantification of human learning. Typifying these efforts, the Rescorla-Wagner model proposed that humans learn associations between stimuli, actions, and consequences by updating their expectations from prediction errors. This and similar models enable researchers to identify neuronal biases in learning that mark many neuropsychiatric disorders but fail to describe important phenomena, notably the rapid return of fear after extinction. To address this shortfall, evidence has converged on the idea that learning agents rely on latent-state inferences, i.e. an ability to form and maintain beliefs over competing hypotheses. By matching current to prior context, latent-state inferences provide an efficient way to learn but could be problematic if overgeneralized (e.g., alleys are dangerous ergo every place outside is dangerous). Indeed, recent research has suggested the utility of latent state learning models to explain superordinate processes encoded in important neural structures in psychiatry, such as the orbitofrontal cortex and the hippocampus. As a specific example, deficits encoding latent states in the orbitofrontal cortex and hippocampus may explain fear extinction recall deficits in PTSD. Accordingly, the study of latent-state inferences is an important area of inquiry in psychiatry and cognitive neuroscience but is limited by modeling frameworks that do not generalize across learning paradigms or impose unrealistic demands on human computation. We thus sought a framework that is more realistic, generalizable, and can help unify computational study of learning.

Methods: We developed a computational model of latent-state inferences, using the Rescorla-Wagner model as its foundation. In a series of simulation experiments, we test the model's ability to reproduce learning experiments both famously explained and not explained by the Rescorla-Wagner model and to capture behavior in recent experiments designed to test latent-state inferences. We then use a novel dataset ($N = 57$) of a learning and decision-making task to determine to what extent our latent-state model better explains participant behavior than the Rescorla-Wagner model and provides consistent parameter estimates. Lastly, we formally derive our latent-state model under the premise of computational rationality, i.e. a learning agent wants to predict outcomes efficiently.

Results: Our latent-state model is shown in simulation to explain the same learning phenomena as the Rescorla-Wagner model such as blocking, overexpectation, and conditioned inhibition and to go beyond the Rescorla-Wagner model's capabilities to explain other phenomena such as backwards learning and Pearce-Hall effect. The latter effort is captured because latent-state inferences allows one to correctly detect the shift in experimental conditions and quickly adjust expectations. Our latent-state model also captures recent experiments of latent-state inferences, including explicitly weighing hypotheses and the rapid return of associations from a prior context and. Using our novel dataset, we demonstrate our latent-state model, with only one additional parameter, better explains participant behavior than the Rescorla-Wagner model (average increase in log-likelihood: 7.9 [95% CI: 6.3-9.5]) yet still returns comparable parameter estimates ($R \geq 0.77$). Lastly, we derive our latent-state model (as well as the Rescorla-Wagner model) as an online algorithm to maximization likelihood estimation, showing that it is indeed a relatively efficient approach to outcome prediction.

Conclusions: We have established the validity of an online model for latent-state inferences that generalizes across experiments and can unify traditional associative learning with latent-state inferences. Establishing such a framework is a necessary step towards quantifying normative and pathological ranges of latent-state inferences (and mediating neurocircuitry) across varied contexts. Overall, this effort moves us closer to precise and mechanistic understanding of biases of human learning in neuropsychiatric disorders.

Keywords: Inference and Learning, Computational Psychiatry, Computational Modeling, Extinction Memory Recall

Disclosure: Nothing to disclose.

W172. Investigating Relationships Between Combat PTSD, Cortical Thickness and Physical Health in Veterans

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Background: An estimated 23 percent or approximately 1,150,000 veterans who have served as part of Operation's Enduring (OEF) and Iraqi (OIF) Freedom develop posttraumatic stress disorder (PTSD) following combat. PTSD has been linked to alterations in brain health including reductions in grey matter volume, changes in white matter integrity, dysregulation in functional activity and connectivity, and to a lesser extent decreased cortical thickness – particularly within the prefrontal cortex. Cortical thickness is used to estimate the combined thickness of the cerebral cortex, which is a proxy for neuronal density. Cortical thinning, a decrease in cortical thickness, in healthy controls is associated with decreased cognitive abilities, and has more recently been linked to PTSD diagnosis and severity. Given that research is still emerging, little is known about underlying mechanisms linking PTSD and decreased cortical thickness. One potential mechanism may relate to physical health, particularly cardiac and metabolic systems. Individuals with PTSD are at an increased risk relative to individuals without PTSD to develop cardiovascular disease and metabolic disorders. Prior research has independently established relationships between decreased cortical thickness and cardiometabolic disorders including atherosclerosis, renal disease, and diabetes. The present study sought to clarify intersecting relationships between combat

PTSD, physical health diagnosis, and cortical thickness in a sample of OEF/OIF veterans.

Methods: Subjects were recruited as part of the Post Deployment Mental Health Study and included male (n = 178) and female (n = 39) veterans (mean age = 38, SD = 10.2), who served since the onset of OEF, and completed clinical and neuroimaging assessments. The clinical assessment included the Structured Clinical Interview for DSM-IV Disorders (PTSD), National Vietnam Veterans' Readjustment Study medical questionnaire - physical diagnosis subscale (physical health diagnosis), and Alcohol Use Disorders Identification Test (current alcohol use). High resolution T1-weighted anatomical scans optimized for tissue contrast were acquired on a 3 T GE MR750 scanner. Autosegmentation of cortical thickness was completed using FreeSurfer (version 5.6.0), segmenting 154 regions. Whole brain QDEC analysis was used to identify regions in which cortical thickness related to PTSD diagnoses controlling for age. Analysis of variance and hierarchical regression analyses were conducted based on whole brain findings to examine relationships between 1) PTSD and regional cortical thickness, 2) physical health diagnosis and cortical thickness and, 3) PTSD, cortical thickness and physical health diagnosis. Moderation analyses were controlled for age, gender and current alcohol use.

Results: Sixty-nine subjects met criteria for current PTSD and 100 endorsed at least one physical health diagnosis. Whole brain analysis revealed subjects with PTSD exhibited lower cortical thickness within 18 brain regions including those within the frontal, and parietal lobes, and increased cortical thickness in 4 regions within the bilateral temporal, right occipital, and right posterior aspect of the superior frontal lobe compared to those without PTSD. Follow-up analysis of regional cortical thickness revealed physical health diagnosis was associated with lower cortical thickness within the right anterior occipital sulcus ($F(1,216) = 4.77$, $p = 0.030$), left inferior angular parietal gyrus ($F(1,216) = 7.29$, $p = 0.007$), left inferior triangular frontal gyrus ($F(1,216) = 11.08$, $p = 0.001$) and left inferior temporal sulcus ($F(1,216) = 10.61$, $p = 0.001$). Regression and moderation analyses controlling for age, gender, and alcohol use, revealed subjects with a physical health diagnosis exhibited lower cortical thickness within the left inferior temporal sulcus ($B = -0.09$, $p = 0.008$); neither PTSD ($B = -0.09$, $p = 0.008$) nor the interaction effect ($B = 0.01$, $p = 0.868$) related to cortical thickness in this region. There was an interaction effect of PTSD and physical health diagnosis within the triangular aspect of the inferior frontal gyrus ($B = 0.11$, $p = 0.026$), suggesting those with a physical health and PTSD diagnosis showed reduced cortical thickness within this region. No main effects were identified for PTSD ($B = -0.01$, $p = 0.583$) or physical health diagnosis ($B = -0.01$, $p = 0.656$) within the triangular aspect of the inferior frontal gyrus.

Conclusions: Present results indicate PTSD is related to decreased cortical thickness bilaterally within the frontal and parietal regions and increased cortical thickness primarily within the temporal and occipital lobes in OEF/OIF veterans. Of those regions associated with PTSD, physical health related to decreases within the right anterior occipital lobe, and lateralization of decreased cortical thickness within the frontal, parietal and temporal lobes within the left hemisphere. Further, results provide initial evidence that veterans who endorsed both PTSD and a physical health diagnosis exhibited decreased cortical thickness within the inferior frontal gyrus. Our results suggest this region, implicated in cognitive processing and control of emotional information, may be particularly susceptible to cortical thinning associated with PTSD and physical health. Longitudinal research is warranted to clarify whether cortical thinning represents a risk factor or sequelae of PTSD.

Keywords: Cortical Thickness, Combat PTSD, Veterans, Human Neuroimaging

Disclosure: Nothing to disclose.

W173. Significant Shared Heritability Underlies Suicide Attempt and Clinically Predicted Probability of Attempting Suicide

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Background: Suicide accounts for nearly 800,000 deaths per year worldwide with rates of both deaths and attempts rising. Family studies have estimated substantial heritability of suicidal behavior; however, collecting the sample sizes necessary for successful genetic studies has remained a challenge.

Methods: We utilized two different approaches in independent datasets to characterize the contribution of common genetic variation to suicide attempt. The first is a patient reported suicide attempt phenotype from genotyped samples in the UK Biobank (337,199 participants, 2,433 cases). The second leveraged electronic health record (EHR) data from the Vanderbilt University Medical Center (VUMC, 2.8 million patients, 3,250 cases) and machine learning to derive probabilities of attempting suicide in 24,546 genotyped patients.

Results: We identified significant and comparable heritability estimates of suicide attempt from both the patient reported phenotype in the UK Biobank ($h2SNP = 0.035$, $p = 7.12x10\text{-}4$) and the clinically predicted phenotype from VUMC ($h2SNP = 0.046$, $p = 1.51x10\text{-}2$). A significant genetic overlap was demonstrated between the two measures of suicide attempt in these independent samples through polygenic risk score analysis ($t = 4.02$, $p = 5.75x10\text{-}5$) and genetic correlation ($rg = 1.073$, $SE = 0.36$, $p = 0.003$). Finally, we show significant but incomplete genetic correlation of suicide attempt with insomnia ($rg = 0.34 - 0.81$) as well as several psychiatric disorders ($rg = 0.26 - 0.79$).

Conclusions: This work demonstrates the contribution of common genetic variation to suicide attempt. It points to a genetic underpinning to clinically predicted risk of attempting suicide that is similar to the genetic profile from a patient reported outcome. Lastly, it presents an approach for using EHR data and clinical prediction to generate quantitative measures from binary phenotypes that can improve power for genetic studies.

Keywords: Suicidal behavior, Human Genetics, Electronic Medical Record, machine learning

Disclosure: Nothing to disclose.

W174. Dynamic Control of Synaptic Organizers – Shaping Protein Interaction Networks in the Synaptic Cleft

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Background: Alpha-neurexins are 'synaptic organizers' implicated in neuropsychiatric disorders, such as autism spectrum disorder and schizophrenia. They form a large family of cell surface molecules, diversified through alternative splicing; and they play an essential role in synapse development as well as promoting synaptic transmission. Alpha-neurexins are tethered predominantly to the presynaptic membrane, and their extracellular domains interact with many partners in the synaptic cleft, including neuroligins, LRRTM family members, calsyntenin 3, alpha-dystroglycan, latrophilin, cerebellins, neurexophilin, IgSF21, and the GABAA-receptor. Neurexins and their partners are

thought to selectively impact the development of excitatory synapses versus inhibitory synapses and malfunctioning of these molecules leads to an imbalance in excitation versus inhibition, disrupting neural circuits critical for cognition and behavior. Crystal structures have shown that the extracellular region of neurexin 1alpha (n1alpha) (containing six LNS domains L1-L6 interspersed by three Egf-like repeats) forms an L-shaped, largely rigid molecule. It is not known how n1alpha fits into the narrow confines of the synaptic cleft yet also recruits its large, membrane-bound partners. Internal molecular flexibility could provide a solution; however, this is challenging to delineate because currently no structural methods permit high resolution structure determination of large, flexible, multi-domain protein molecules like n1alpha.

Methods: We used a combination of structural and biophysical methods to gain insight into the conformational variability of n1alpha. We used electron microscopy and electron tomography (ET) to probe the architecture of the full-length n1alpha ectodomain. We used crystallography to examine the conformation of the n1alpha L2-L3 fragment and to test for the presence of a molecular switch. Finally, we examined the effects of an alternative splice insert on the conformation of n1alpha L5-L6.

Results: Individual particle electron tomography (IPET) revealed that the N-terminally and C-terminally tethered domains, L1 and L6, have a surprisingly limited range of conformational freedom with respect to the linear central core containing L2 through L5. A 2.8 Å crystal structure revealed an unexpected molecular switch between the L2 and L3 domains. SAXS and ET indicated that incorporation of an alternative splice insert relieves the restricted conformational freedom between L5 and L6, suggesting that it works as a molecular toggle.

Conclusions: Our data suggest that the architecture of n1alpha encodes a combination of rigid and flexibly tethered domains that are uniquely poised to work together to promote its organizing function in the synaptic cleft and may permit allosterically regulated and/or concerted protein partner binding. By elucidating structure-function relationships of molecules that guide inhibitory and/or excitatory synapse development we hope in future to identify new therapeutic targets that could be leveraged for the treatment of neuropsychiatric disorders.

Keywords: Neurexins, Synaptic Organizers, Protein Conformations, Synaptic Protein Interaction Networks, Protein Dynamics

Disclosure: Nothing to disclose.

W175. A Neuron-Optimized CRISPR/dCas9 Activation System for Robust and Specific Gene Regulation

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Background: Gene expression patterns define neuronal phenotypes and are dynamic regulators of neuronal function in the developing and adult brain. During development, differential expression of transcription factors induces gene programs responsible for neuronal fate specification and maturation. In the adult brain, specific gene programs are altered by neuronal activity and behavioral experience, and these changes are critical for adaptive behavior. Dysregulation of both developmental and adult brain gene programs is implicated in numerous neuropsychiatric diseases, such as addiction, depression, schizophrenia, and Alzheimer's disease. Recent developments in CRISPR-based gene editing have provided new avenues to interrogate gene function, including unparalleled control of genetic sequences, transcriptional states, and epigenetic modifications. However, application of these tools in the central nervous system has been delayed due to difficulties in transgene expression in post-mitotic neurons.

Methods: We engineered a highly efficient, neuron-optimized dual lentiviral CRISPR-based transcriptional activation (CRISPRa) system to drive gene expression in primary neuronal cultures and the adult brain of rodent model systems. We combined CRISPR/dCas9 transcriptional activation with genome-wide transcriptional profiling, multi-electrode array electrophysiology, and stereotaxic viral delivery to examine the efficacy of this tool at multiple gene targets and in multiple neuronal subtypes.

Results: Using primary neuronal cultures, we demonstrate that our neuron-optimized CRISPRa system enables robust upregulation of a wide variety of genes that are critical for neuronal processes, including genes of various lengths, cellular roles, and physiological functions. This optimized CRISPRa system is effective in multiple neuronal populations, including cortical, hippocampal, and striatal neurons. Moreover, multiplexed pooling of CRISPR guide RNAs enables synergistic upregulation of a single target or coordinated control over many genes. CRISPRa targeting individual transcript promoters in Brain-derived neurotrophic factor (Bdnf) – a complex gene involved in synaptic plasticity, learning, and memory – revealed highly specific Bdnf transcript control without impact at non-targeted variants or predicted off-target sites. Targeted Bdnf transcript upregulation resulted in downstream regulation of genes implicated in neuronal physiology, and also increased neuronal activity and burst firing, demonstrating the efficacy of this approach for studying downstream transcriptional programs and physiological functions. Finally, we illustrate that CRISPRa is highly efficient in vivo, resulting in increased protein levels of a target gene in diverse brain structures.

Conclusions: Our results indicate that this neuron-optimized CRISPRa system enables modular, multiplexed control of gene expression profiles within the CNS to elucidate the role of gene expression in neuronal function, behavior, and neuropsychiatric disorders.

Keywords: CRISPR/dCas9, BDNF, Gene Transcription

Disclosure: Nothing to disclose.

W176. Investigation of rs-fMRI Entropy as a Biomarker of Visual System Deficits in Combat Veterans

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Background: Each year, mild traumatic brain injury (mTBI) impacts the lives of an estimated 5 million Americans and is one of the signature injuries of troops wounded in battle fields across the world. Visual symptoms are common sequelae of mTBI. Little is known about the chronic, visual consequences of mTBI, its progression, and its correlation with central nervous system (CNS) dysfunction. Currently, it is not known if neuronal loss in the retina and brain after mTBI continues to progress. We hypothesize that, after mTBI, structural and functional patterns of damage in the visual system are more prevalent than previously appreciated and that these biomarkers can serve to identify and predict dysfunction in the CNS as a whole. Our hypothesis is based on strong preliminary data from our studies in humans, and in established animal models of mTBI, which show that acute injury initiates visual pathway damage, leading to a chronic, progressive process of neural degeneration.

Methods: Participants with and without a history of mild TBI undergo functional and structural MRI scans, cognitive and clinical

tests, and evaluation of visual function and ocular motility. Good quality resting state fMRI data were collected for 120 subjects. Data were preprocessed using FSL tools, including motion correction, dewarping and alignment to standard MNI space via individual structural T1's. We assessed bivariate (strength and diversity) and multivariate (largest connected component, clustering coefficient) graph theoretical metrics for each subject, computed using wavelet filtered correlation matrices. Specifically, for each ROI's time-series, the rs-fMRI data was filtered in Matlab using a discrete wavelet transform prior to the creation of correlation matrices. Additionally, entropy was calculated for specific regions implicated in the visual system, with an emphasis on primary visual cortex (V1), the lateral geniculate cortex (LGN), fusiform gyrus, and medial prefrontal cortex. Entropy is a univariate measure of signal complexity that is well characterized in information theory and has been previously used to quantify different brain states.

Results: No significant differences in rs-fMRI bivariate or multivariate graph theoretical metrics were found between controls ($n = 60$) and mTBI patients ($n = 60$). However, a preliminary entropy analysis across groups ($n = 75$) revealed a strong correlation between entropy in the primary visual cortex and entropy in the medial prefrontal cortex ($R = 0.54$, $p < 0.001$).

Conclusions: Our preliminary analyses sought to explore biomarkers of mTBI insult to the visual system and its relationship to dysfunctions in other parts of the brain. Our findings suggest that entropy in early visual areas may influence entropy in top-down areas of the visual system such as the prefrontal cortex. Further investigation comparing entropy in the visual system with retinal thickness measures will be critical for better understanding the utility of entropy as a biomarker for mTBI.

Keywords: Graph-based Analysis, Entropy, Functional MRI (fMRI), TBI, Visual

Disclosure: Nothing to disclose.

W177. Phenotypic Landscape of Schizophrenia-Associated Genes Defines Candidates and Their Shared Functions

Abstract not included.

W178. Developmental Regulation of Neuronal Chloride Homeostasis and the E/I Switch: Interaction of NRG1 Genetics and Perinatal Choline Supplementation

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Background: Genes involved in maturation of GABAergic neurotransmission, including Neuregulin1 (NRG1,[8p21-p12]) and CHRNA7 [15q13.3], are associated with neurodevelopmental disorders, including schizophrenia (SZ). Identification of the ontogenic mechanisms is crucial for understanding pathogenesis and primary prevention advances. Our studies in human brain have demonstrated that a molecular mechanism of genetic risk in NRG1, in SZ involves rs6994992, a promoter polymorphism associated with elevated transcription of the NRG1 isoform, (NRG1-IV) and reduced brain levels of the CHRNA7 receptor (α7nAChR). Signaling via the α7nAChR is a critical driver of the GABA excitatory/inhibitory (E/I) shift, mediated via the chloride cotransporters, NKCC1 and KCC2; and deficits in α7nAChR expression are a potential mechanism of observed increases in the NKCC1/KCC2 ratio in SZ patients and associated E/I deficits. NRG1 is a regulator of α7nAChR expression; the role of NRG1-IV is unknown. Choline is a α7nAChR agonist, and a novel prenatal supplementation strategy in humans shown to improve early childhood behaviors' relevant to later SZ; the neuromolecular mechanisms are unknown. Here we studied the developmental transcriptional regulation of the NKCC1/KCC2 switch in mPFC of NRG1-IVtgNSE-tTA (male and female) transgenic mice, and assessed the impact of perinatal α7nAChR agonism, via maternal dietary choline supplementation.

Methods: We developed a transgenic mouse (NRG1-IVtgNSE-tTA) engineered to overexpress human NRG1-IV exclusively in brain. mPFC was used for quantitative RNA profiling to assess the developmental trajectories of NKCC1 & KCC2 expression. Mice at postnatal (P) days, P0, P6, P9 and P13 were studied, either exposed to a normal (1 g/kg) or choline-supplemented (5 g/kg) maternal diet during gestation through weaning.

Results: In male and female mice exposed to a standard choline diet, a main effect of postnatal age was observed on the NKCC1/KCC2 ratio ($N = 102$; ANOVA, $p < 0.0001$), whereby NKCC1/KCC2 ratios were dramatically higher at P0, declining to reach adult levels by P13. These molecular data parallel the developmental shift in GABA E/I balance. An interaction of sex*age was observed on the NKCC1/KCC2 ratio (ANOVA, $p = 0.002$) with all female mice showing higher ratios than males at P0. All mice exposed to maternal dietary choline supplementation showed developmental acceleration of the molecular switch (main effect of diet; $N = 183$; ANOVA, $p < 0.0001$), with both NRG1-IVtgNSE-tTA and control choline-supplemented mice exhibiting significantly lower NKCC1/KCC2 ratios at P0. Finally, male and female NRG1-IVtgNSE-tTA exposed to a normal choline diet showed elevated NKCC1/KCC2 expression ratios ($n = 27$, $p < 0.05$), at P13, when the molecular switch is complete, and similar to findings observed in adult patients with SZ. Maternal gestational choline supplementation prevented this deficit resulting in normalization of the ratio in NRG1-IVtgNSE-tTA mice ($n = 17$, main effect of genotype $p = 0.885$).

Conclusions: Our data demonstrate a novel biogenetic interplay between NRG1-IV, CHRNA7 and developmental regulation of the NKCC1/KCC2 switch, necessary for maturation of E/I balance. We show that a molecular mechanism of choline's effects in utero, involves accelerated maturation of neuronal chloride homeostasis, via altered regulation of NKCC1/KCC2 transcription.

Keywords: NKCC1, neuregulin-1, Cortical GABA, Genetic Mouse Model

Disclosure: Nothing to disclose.

W179. Longitudinal Multimodal Neuroimaging in a Non-Human Primate Cohort With Maternal Immune Activation: Changes in Brain Structure, Free Water and Neurochemistry During the First Year of Life

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Background: Epidemiological studies have revealed an association between maternal infections and risk of psychotic illness in the offspring, while neuroimaging and post mortem studies of patients with schizophrenia suggest that perturbations in neuroimmune mechanisms may be related to the pathophysiology of the illness. Mouse and rat models of maternal immune activation (MIA) show a characteristic pattern of altered cognitive and social behavioral phenotypes in adolescence that follows a period of typical development, along with the presence of

changes in brain structure and chemistry, including increased sensitivity to dopamine agonists. In a previous pilot study, a small cohort of rhesus macaques was treated with Poly IC: IC during first or second trimester of pregnancy. Like their rodent counterparts, offspring showed altered social behaviors during adolescence following a window of typical development. These animals also showed increased presynaptic dopamine levels in the striatum using FMT PET. As part of the UC Davis Conte Center focusing on neuroimmune mechanisms in psychiatric disorders, a new, MIA NHP cohort has undergone longitudinal MRI and PET studies examining brain structure, free water and striatal dopamine levels. Here we present initial results from the first year of life.

Methods: 24 pregnant rhesus macaques carrying male fetuses were randomly assigned to MIA (polyIC:IC, n = 14) or control (n = 10 saline) treatment at the end of the first trimester. Untreated male offspring were added to the control group (n = 4) and all offspring were characterized behaviorally and using MRI imaging at 6 months and 12 months of age. Data were acquired on a Siemens 3 T Skyra scanner using custom head coils under isoflurane anesthesia. Free water data were acquired using a multi-shell diffusion weighted pulse sequence. In a separate PET scanning session 18 F]fluoro-l-m-tyrosine (FMT) was used to measure striatal dopamine synthesis capacity. Animals were injected with benzeracide (2 mg/kg) 30 mins prior to FMT injection. Structural T1 and T2 weighted images were processed using multi-atlas segmentation in the AutoSeg and NeosegPipeline toolbox. Volumes (mm3) were derived for particular hypothesis-driven bilateral regions of interest (ROI): prefrontal, frontal, anterior cingulate and temporal limbic cortices, as well as amygdala and hippocampus. Group differences in ROI volumes at 6 and 12 months were investigated using linear mixed effect models.

Results: MIA Dams showed expected increases in temperature and sickness behavior as well as increases inIL6 and other pro-inflammatory cytokines. No differences in motor or reflex development, growth trajectories, or home cage observations during the 12-month period were observed between MIA and control animals. Across the two time points, gray matter volumes were reduced in PolyIC:IC animals in left prefrontal, frontal and left anterior cingulate cortex (all $p < .05$). Significantly increased free water measures were observed in MIA monkeys for cingulate cortex ($p < .05$) as well as trend level increases in frontal and temporal limbic cortices ($P < .06$). No differences between groups were observed for white matter FW or striatal presynaptic dopamine at 1 year of age.

Conclusions: MIA in rhesus macaques leads to structural changes (reduced frontal gray matter volumes) and increases in measures of gray matter free water in the anterior cingulate cortex early during post-natal development. Similar abnormalities have been previously observed in individuals with schizophrenia and those at clinical high risk for the illness. These results are consistent with the presence of changes in brain structure and function prior to the onset of overt behavioral pathology and hyperdopaminergia in this novel non-human primate developmental model of psychosis, and also highlight the potential predictive utility of non-invasive neuroimaging biomarkers in young, at risk human populations. Ongoing imaging and behavioral studies of these animals tracking the first 4 years of life will further inform these results going forward.

Keywords: Non-Human Primate, Neurodevelopment, Neuroimmune Mechanisms, Schizophrenia, Longitudinal Multimodal Imaging

Disclosure: Nothing to disclose.

W180. Deficiency of Schnurri-2 Disrupts Auditory Event Related Potentials Due to Augmentation of the Basal Power of EEG

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Background: The deficiency of Schnurri-2 (Shn-2), nuclear factor-kappa B (NF-kB) site-binding protein that is known to regulate immune-related gene expression through the binding with major histocompatibility complex, has been observed in some cases of psychiatric disorders, including schizophrenia and developmental disorders. This raises a possibility that activated immune responses through NF-kB could underlie pathophysiology of psychosis. Indeed, Shn-2 homozygous knockout (KO) mice demonstrate molecular and morphological phenotypes related to schizophrenia as well as robust neuroinflammation in the brain. Behaviorally Shn-2 KO mice display several impairments reminiscent to psychiatric disorders. Taken together, Shn-2 KO mouse is an attractive rodent model of psychiatric disorders presenting neuroinflammation. In the present study, we explored to identify translatable biomarkers in Shn-2 KO mice. Power spectrum analysis in electroencephalogram (EEG) and EEG-detectable event-related potentials have been proven to be useful in detecting neurophysiological features and sensory processing deficits in patients with psychiatric diseases. Alterations in basal theta and gamma frequencies and auditory event-related potentials (ERPs) have been well reported as one of translational science tools for patient stratification in the field of psychiatry. Thus, we assessed neurophysiological phenotypes in Shn-2 KO mice by using quantitative EEG and ERPs analysis.

Methods: Wild type (WT) and Shn-2 homozygous KO mice were surgerized for implantation of a tripolar electrode and used for this investigation. A positive electrode was placed in CA3 subregion of hippocampus of the right hemisphere (AP; -1.9 mm, ML; 2.5 mm, Depth; -2.6 mm from bregma). Reference and ground electrodes were placed on the surface of the brain. Animals were housed singly and allowed to recover for at least 2 weeks prior to EEG recording. Using Spike 2 software, two of EEG recording paradigms, inter stimulus interval (ISI) and mismatched negativity (MMN) were generated. The ISI is composed of 5 blocks of intervals (0.5, 1, 2, 4, and 8 sec) and each block contains 200 single click sound stimuli at 85 dB. The MMN is composed of 4 KHz and 12 KHz tones for standard and deviant stimuli, respectively, at 85 dB. Basal power, ERPs, and MMN were analyzed using EEGLAB, a MATLAB (MathWorks) toolbox.

Results: Despite severe behavioral deficits, Shn-2 KO mice were able to produce EEG wave forms similar to WT mice. The basal power in resting EEG recording significantly augmented in all bands of frequencies (0-80 Hz) in Shn-2 KO mice in comparison to WT mice. Theses augmentation were persistently present in each ISI paradigm. In Shn-2 mice, increases in ERPs such as N1 and P2 were observed in response to auditory stimuli in ISI ranging from 1 to 8 sec, although no changes were detected in 0.5 sec ISI. The latency of N1 and P2 were also altered in ISI from 1 to 8 sec, but not at 0.5 sec ISI. In 8 sec ISI, Shn-2 KO mice showed significantly decreased amplitude of N1 and delayed latency of N1 and P2. In time-frequency analysis of 8 sec ISI, event related spectrum perturbation (ERSP) in Shn-2 KO mice exhibited a significant increase in power of evoked/induced theta, and reduction of powers of evoked/induced gamma. The ITC indicated significantly reduced power of evoked gamma. In the MMN paradigm, Shn-2 KO mice also showed abnormally higher responses compared to WT mice without any changes in ERPs by standard stimuli.

Conclusions: This is the first report on neurophysiological profiling of Shn-2 homozygous KO mice with auditory ERPs. Our results demonstrate that the lack of Shn-2 gene causes aberrant auditory sensory processing, most pronouncedly augmentation of the basal power across all the frequency bands. These abnormal alterations in the basal power and auditory ERPs could serve as useful biomarkers to enrich and/or stratify psychiatric patients with exacerbated neuroinflammation in the brain.

Keywords: Schnurri-2 Knockout Mice, EEG/ERP Electrophysiology, MMN, ISI

Disclosure: Astellas Pharma Inc, Employee

W181. Kinase Network Dysregulation in a Human Induced Pluripotent Stem Cell Model of DISC1 Schizophrenia

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Background: Protein kinases orchestrate signal transduction pathways involved in central nervous system functions ranging from neurodevelopment to synaptic transmission and plasticity. Abnormalities in kinase-mediated signaling are involved in the pathophysiology of neurological and neuropsychiatric disorders, including schizophrenia. Here, we expand on the hypothesis that kinase networks are dysregulated in schizophrenia. We investigated changes in serine/threonine kinase activity in cortical excitatory neurons differentiated from induced pluripotent stem cells (iPSCs) from a schizophrenia patient presenting with a 4-bp mutation in the disrupted in schizophrenia 1 (DISC1) gene and a corresponding control.

Methods: We analyzed kinase activity in human iPSC cell lines differentiated into frontal cortical neurons using the Pamgene Kinome array platform, as well as a new software program developed in house (called KRSA) > We also used published and unpublished databases to perform look up replication studies of our findings. Finally, we used the LINCS database to identify possible drug leads that reverse the Kinome signature associated with our schizophrenia samples.

Results: Using kinome peptide arrays, we demonstrate large scale abnormalities in DISC1 cells, including a global depression of serine/threonine kinase activity ($P < 0.05$), and changes in activity of kinases, including AMP-activated protein kinase (AMPK), extracellular signal-regulated kinases (ERK), and thousand-and-one amino acid (TAO) kinases. Using isogenic cell lines in which the DISC1 mutation is either introduced in the control cell line, or rescued in the schizophrenia cell line, we ascribe most of these changes to a direct effect of the presence of the DISC1 mutation. Investigating the gene expression signatures downstream of the DISC1 kinase network and mapping them on perturbagen signatures obtained from the Library of Integrated Network-based Cellular Signatures (LINCS) database, allowed us to propose novel drug targets able to reverse the DISC1 kinase dysregulation gene expression signature.

Conclusions: Our findings provide new insight into abnormalities of kinase networks in schizophrenia and suggest possible targets for disease intervention.

Keywords: Schizophrenia, Kinome, Signal Transduction, Pluripotent Stem Cells

Disclosure: Nothing to disclose.

W182. Circuit Specific Single-Nucleus RNA Sequencing of Postmortem Human Hippocampus in Schizophrenia and Bipolar Disorder

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Background: Multiple molecular studies of homogenized postmortem human brain tissue have identified disrupted GABA signaling in schizophrenia and bipolar disorder, and downregulation of the GAD1 gene is among the most widely replicated findings in molecular studies of these disorders. Emerging technologies for single-cell transcriptomics now allow for high-throughput assessment of how the GABAergic deficit is partitioned across distinct neuronal circuitry and GABAergic interneuronal subpopulations, advancing our understanding of circuitry-based information processing and its dysfunction in psychotic illness.

Methods: Subfield CA1 and CA3 specific postmortem human hippocampus tissue samples were microdissected from a cohort matched for age, gender, and postmortem interval from 10 schizophrenia, 10 bipolar disorder, and 10 control subjects. Samples were multiplexed for nuclear isolation and FACS purification of neuronal nuclei, followed by single-nucleus RNA sequencing experiments on the 10X Genomics Chromium platform. Data was deconvoluted using genotype information generated with the Illumina OmniExpress BeadArray.

Results: Preliminary data analysis reveals phenotypic variation between common neuronal subtypes across circuit locations. Comparison of diagnostic groups identifies cell-type specific differential expression, with multiple GABA signaling relevant genes impacted in multiple neuronal populations. Diagnosis associated phenotypic shifts in specific cell-types in separate subfields overlap to a considerable extent but do show circuit-location distinctions, with subfield CA3 more heavily impacted than CA1.

Conclusions: Advances in single-cell genomics technologies promise to revolutionize our knowledge of the "parts list" of the cellular machinery of the human brain, as well as how molecular pathologies are distributed among those functional units in psychiatric illness. This ongoing project demonstrates the power of assessing single-cell transcription in physically microdissected circuit locations within the human brain to elucidate the molecular pathology of psychotic disorders at a resolution not previously possible, offering insights into how this pathology operates within the complex cytoarchitecture of the human brain.

Keywords: Postmortem Brain Tissue, Single-cell RNA Sequencing, Hippocampal Subfields, Schizophrenia, Bipolar I disorder

Disclosure: Nothing to disclose.

W183. Drug Discovery for Schizophrenia Using an Evidence-Based Approach

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Background: Over the past decades drug development in schizophrenia has included repurposing drugs approved for other indications, based on scientific hypotheses. However, the majority of these studies have been unsuccessful. We approached drug repurposing in schizophrenia with a data driven, not hypothesis-driven strategy. We utilized VA administrative encounter data, which includes prescription records and data on psychiatric

hospitalizations, on approximately 100,000 veterans with schizophrenia and 240,000 with bipolar disorder. The objective of this study was to identify non-psychiatric drugs associated with a decreased number of psychiatric hospitalizations after initiation of treatment.

Methods: Data source: This study used VA administrative data from 2011-2015. These data consist of records for all inpatient and outpatient health care services, demographics, diagnoses and prescription medications dispensed. This study was approved by the University of Maryland School of Medicine IRB. The sample included 101,434 Veterans with schizophrenia.

Medication screening: We first reviewed the VA's pharmacy formulary and eliminated 1,278 topical medications, wound care agents, blood and other parenteral products, diagnostic agents, intrapleural medications, and antidotes/antivenoms. This led to an initial screening of 823 non-psychotropic medications.

To ensure that analyses included medications with sufficient sample sizes of individuals with an adequate exposure period, we identified those agents that were prescribed to at least 100 individuals with schizophrenia for at least 3 consecutive months during the study period.

We identified 156 medications prescribed to at least 100 individuals with schizophrenia who had incident episodes lasting at least 3 consecutive months. For each drug, we examined the unadjusted difference in the rate of psychiatric hospitalization in the 6 months before versus the 6 months after the start of the incident episode. From this group, isoniazid, two non-sedating antihistamines (cetirizine, loratadine) and several non-steroidal anti-inflammatory medications (diclofenac, etodolac, ibuprofen, meloxicam, naproxen, salsalate) were judged by the study team to merit further investigation based on their potential impact on psychiatric hospitalization, their mechanisms of action, and on previous investigations for the treatment of schizophrenia. We performed preliminary within-group ('mirror image') analyses, adjusted for age, gender, and antipsychotic coverage. Analyses for two of the medications, etodolac and salsalate, were not statistically significant and thus were not included in subsequent analyses.

In a final step, we conducted propensity-score weighted comparative analyses for the remaining 7 medications to determine their effects on psychiatric hospitalization. The comparison groups for each of these drugs consisted of individuals prescribed non-psychotropic medications from a different class than the drug of interest and that were prescribed to at least 100 people with incident episodes lasting at least 3 months. We conducted sensitivity analyses substituting psychiatric emergency room visits as the outcome and repeating all analyses in individuals with bipolar disorder.

Results: The results of the adjusted comparative analyses for cetirizine, loratadine, diclofenac, ibuprofen, and meloxicam were not statistically significant.

Isoniazid: For those prescribed isoniazid (n = 211), the odds of psychiatric hospitalization in the 6 months following the start of the incident episode was 0.39 (95% CI: 0.22 – 0.69) of the odds in the 6 months before the episode began (~61% reduction). In the comparison group (n = 51,301), the odds of psychiatric hospitalization in the 6 months following the start of the incident episode was 0.73 (95% CI: 0.71 -0.75) of that in the prior 6 months (~27% reduction). The reduction in odds among those who were prescribed isoniazid was significantly greater than among those who weren't (Wald Chi-square = 4.55, df = 1, p = .0328). The results of sensitivity analyses were generally consistent with these findings.

Naproxen: For those who were prescribed naproxen (n = 2,083), the odds of psychiatric hospitalization in the 6 months following the start of the incident episode was 0.67 (95% CI: 0.56 – 0.79) of the odds in the 6 months before the episode began (~33% reduction). In the comparison group (n = 50,476), the odds of psychiatric hospitalization in the 6 months following the start of the incident episode was 0.79, (95% CI: 0.78 -0.81) of that in the prior 6 months (~21% reduction). The reduction in odds among those who were prescribed naproxen was significantly greater than among those who weren't (Wald Chi-square = 3.87, df = 1, p = .0491). The results of sensitivity analyses were generally consistent with these findings.

Conclusions: Administration of isoniazid was associated with decreased risk for psychiatric hospitalizations. Isoniazid crosses the blood brain barrier and inhibits monoamine oxidase, a mechanism which might be related to this finding. The finding that administration of naproxen is associated with decreased risk for psychiatric hospitalization supports studies showing that NSAIDs might be efficacious in treating schizophrenia. Although potential confounders were controlled for, it is conceivable that other unknown factors might be the cause of the observed findings. These data support performing clinical trials for isoniazid and naproxen in schizophrenia.

Keywords: Evidence-Based Approach, Schizophrenia Novel Treatment, Database

Disclosure: Nothing to disclose.

W184. Functional Recovery Among Patients With Schizophrenia Receiving Aripiprazole Once-Monthly in a 52-Week, Open-Label, Maintenance Study

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Background: The primary goal in the treatment of schizophrenia has evolved from acute treatment toward relapse prevention and ultimately recovery. A consensus definition of recovery, however, has not yet been endorsed by the clinical community. The concept of functional recovery in patients whose symptoms are controlled by medications is generally accepted as the ultimate treatment goal. Long-acting injectable atypical antipsychotics give patients with schizophrenia the best opportunity to achieve functional recovery, because they enhance adherence, provide sustained levels of therapeutic plasma drug concentrations, and a lower side effect profile than typical antipsychotic depots.

Here we attempt to operationalize functional recovery using secondary efficacy endpoint data on the personal and social performance (PSP) scale from a long-term (52-week), open-label extension study of aripiprazole once-monthly (AOM) (NCT00731549) [1]. Mean PSP scores and mean change in PSP scores are assessed to determine patients' functional status after up to 52 weeks of treatment with AOM.

Methods: Enrolled patients were 18 to 65 years of age with a current diagnosis of schizophrenia (DSM-IV-TR). Patients were naïve to AOM 400 treatment or previously randomized in one of two controlled trials assessing the efficacy and safety of AOM 400 (NCT00705783 [2], NCT00706654 [3]). Patients were stabilized on treatment during an oral stabilization phase; those meeting predefined stabilization criteria continued to 52 weeks of AOM 400 maintenance treatment. PSP scores were obtained at baseline and end of the oral stabilization period (baseline for 52-week maintenance period), and at Weeks 24 and 52 of the maintenance phase. PSP measures socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviors which are transformed to a 100-point scale. Scores from 71 to 100 represent mild to no functional difficulty, 30 to 70 represent manifest to marked difficulty, and 1 to 30 represent severe difficulty. Patients with scores > = 71 may be considered "functionally recovered". Means and mean change in PSP scores for the

observed case efficacy population are reported with standard deviation (SD).

Results: 1,144 patients entered the oral stabilization phase. 1,069 of these entered the AOM maintenance phase with a mean PSP score of 67 (SD = 13) together with 12 patients who entered the maintenance phase directly after completing one of the parent studies (1081 in total). Of the 1081 entering the maintenance phase, mean PSP scores were 68 (SD = 12). At Week 24, patients had a mean change in PSP score of 1.1 (n = 870, SD = 7.1) with a mean PSP score of 69 (SD = 12). At Week 52, patients had a mean change in PSP of 2.2 (n = 664, SD = 6.6) with a mean PSP score of 70 (SD = 12). Of the 664 completers, 315 (47%) had PSP scores > 70.

Conclusions: Results show maintenance of function after treatment with AOM for up to 52 weeks where the majority of patients completed 52 weeks of treatment. Nearly half of the completers had a PSP score indicating mild to no functional difficulty, adding to the evidence base for positive functional outcomes in patients treated with AOM [4].

Keywords: Aripiprazole Once-Monthly 400 mg (AOM 400), Personal and Social Performance (PSP), Schizophrenia, Antipsychotics

Disclosure: Nothing to disclose.

W185. Significant Improvement in Treatment Resistant Auditory Verbal Hallucinations After 5 Days of Double-Blind, Sham Controlled Inhibitory (cathodal) tDCS to Left Superior Temporal Gyrus: A Replication and Extension Study

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Background: Approximately 30% of schizophrenia (Sz) patients suffer from auditory verbal hallucinations (AVH) that are non-responsive to antipsychotic treatment and may reflect hyperconnectivity between temporo-parieto-occipital junction (TPOJ) and anterior insula. Transcranial direct current stimulation (tDCS) uses low-level (< 2 mA) scalp-applied currents to non-invasively modulate brain function.

Subjects receiving active treatment showed significantly greater percent improvement in hallucinations rated using the Positive and Negative Symptom Scale (PANSS), as reflected in a significant, moderate effect-size main effect of group through one month (p = 0.044, d = 0.46). Significant improvement for subjects receiving active treatment was also seen on the Auditory Hallucination Rating Scale (AHRS) with 20% improvement in the active group vs. 9% in the sham (p = 0.036, d = 0.48). Greatest individual effect was observed on the AHRS loudness subscale (p = 0.001, 0.69). Greater response was also seen in patients on lower doses of antipsychotic medication (p = 0.04, d = 0.55) and those with lower levels of cognitive symptoms (p = 0.028, d = 0.61). In target engagement analysis, suprathreshold mean field strength was obtained within target regions in TPOJ and auditory association (AA) regions. No significant effect of tDCS on persistent negative symptoms was observed. We investigate cathodal tDCS over left TPOJ for antipsychotic-resistant AVH in a double-blind, sham controlled, multicenter study, seeking replication of previous positive studies in the largest study conducted to date. In addition, we explored both patient characteristics and across-subject variations in tDCS-induced field strength to help guide future, definitive investigations.

Methods: 89 subjects were enrolled (active: 47; Sham: 42) across two sites. 79% were outpatients (active: 37; Sham: 33). Participants were randomized to two 20-minute treatments of cathodal stimulation over the left TPOJ and anodal stimulation over the left dorsolateral prefrontal cortex vs. sham tDCS per day over 5 days, following the procedures of previous positive studies. In a subsample in the active group (n = 21), target engagement (local field strength) was analyzed using structural MRI and finite-element modeling.

Results: Subjects receiving active treatment showed significantly greater percent improvement in hallucinations rated using the Positive and Negative Symptom Scale (PANSS), as reflected in a significant, moderate effect-size main effect of group through one month (p = 0.044, d = 0.46). Significant improvement for subjects receiving active treatment was also seen on the Auditory Hallucination Rating Scale (AHRS) with 20% improvement in the active group vs. 9% in the sham (p = 0.036, d = 0.48). Greatest individual effect was observed on the AHRS loudness subscale (p = 0.001, 0.69). Greater response was also seen in patients on lower doses of antipsychotic medication (p = 0.04, d = 0.55) and those with lower levels of cognitive symptoms (p = 0.028, d = 0.61). In target engagement analysis, suprathreshold mean field strength was obtained within target regions in TPOJ and auditory association (AA) regions. No significant effect of tDCS on persistent negative symptoms was observed.

Conclusions: The present report represents the largest study of tDCS for persistent AVH, and the first to map effects relative to target engagement. We replicate previous reports of significant therapeutic benefit, while also identifying symptom domains and patient populations who show the highest likelihood of benefit. Although significant cathodal field strength was obtained within specific TPOJ and AA regions, significant off-target current flow was observed as well. Future studies using high-definition approaches may more precisely target anterior and posterior regions within the AVH network.

Keywords: TDCS, Auditory Hallucinations, Target Engagement

Disclosure: Krog & Partners Incorporated, Honoraria, IQVIA, Honoraria, Alphasights, Honoraria, Kinetix Group, Honoraria, Slingshot, Honoraria, Semantics MR LTD, Honoraria, Transperfect, Honoraria, BVF Partners, Honoraria, Taisho, Grant, Lundbeck, Grant, Boehringer Ingelheim, Grant, NeuroRX, Grant, Teva, Grant, Merck, Grant

W186. Number Needed to Treat and Cohen's d: Translating Trial Endpoints Using Effect Sizes to Communicate Clinical Usefulness, a Re-Analysis of the Pivotal Trial of Aripiprazole Lauroxil for the Treatment of Schizophrenia

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Background: Although great effort is made in clinical trials to demonstrate statistically significant differences when comparing interventions, insufficient attention is paid regarding the clinical relevance of the outcomes. Effect sizes are not always reported. There are many available absolute effect size measures, including Cohen's d, area under the curve, success rate difference, attributable risk, and number needed to treat (NNT). Of these measures, NNT is perhaps the most intuitive to clinicians. NNT helps relate the effect size back to the realities of clinical practice because it is based on binary or dichotomous outcomes (e.g., success vs. lack of success). Also, the magnitude of the NNT effect size is generally consistent with that calculated from the analogous continuous outcome assessed using metrics such as Cohen's d. The metric number needed to harm (NNH) is used when describing unwanted outcomes, such as adverse events. Tradeoffs between benefits and harms can be further quantified

using the ratio of NNH to NNT and is called the likelihood to be helped or harmed (LHH). We demonstrate these concepts in this re-analysis of the pivotal trial of long-acting antipsychotic aripiprazole lauroxil (AL) for the treatment of schizophrenia.

Methods: Categorical efficacy and tolerability data was extracted from the clinical trial database of the Phase 3, pivotal, double-blind, 12-week, placebo-controlled study of AL in persons with an acute episode of schizophrenia. NNT and NNH values were calculated with their respective 95% confidence intervals (CI). LHH was then calculated contrasting therapeutic response vs. undesired tolerability outcomes. The Cohen's d effect size for the primary efficacy outcome was also calculated to assess comparability with the effect sizes calculated using NNT.

Results: Using the Intent-to-Treat Population for the two doses of AL (441 mg [N = 196] and 882 mg [N = 204] every 4 weeks) pooled together, responder rates (≥ 30% improvement from baseline Positive and Negative Syndrome Scale [PANSS] total score) were 35.3% for AL vs. 18.4% for placebo (N = 196), yielding a NNT of 6 (95% CI 5–11). Lower thresholds for response (i.e. ≥ 20% reduction in PANSS total score from baseline to endpoint) evidenced a NNT of 4 (95% CI 3-6) (i.e., a larger effect size), and higher thresholds (≥ 40 or 50%) produced smaller effect size estimates for NNT of response vs. placebo (10 [95% CI 7-20] and 26 [95% CI 14-216], respectively). AL responders using the PANSS total score reduction threshold of ≥ 30% for the pooled AL doses were apparent (i.e., the 95% CI did not encompass infinity), as early as Day 22, where the NNT vs. placebo was 9 (95% CI 6–19). Effect sizes were larger (i.e., NNT lower) at Days 57 and 85, where the respective NNT values were 7 (95% CI 5-12) and 6 (95% CI 5-11). For the subpopulation of patients who had a baseline PANSS total score > 92 (the baseline median), NNT values vs. placebo generally demonstrated a larger effect size compared with the total population at all thresholds and at all time points after Day 8. The NNT estimate was 5 (95% CI 4–8) for pooled doses of AL using the criterion of a PANSS total score reduction of ≥ 30% at endpoint. Discontinuation rates due to adverse events (AEs) were higher for patients randomized to placebo than for either dose of AL, thus LHH could not be meaningfully calculated using that outcome. Akathisia was the only AE with incidence ≥ 5% in each AL group and at least twice the rate of placebo (11.6%, 11.5%, and 4.3% of patients in the AL 441 mg group, 882 mg group, and placebo, respectively), producing a NNH of 14 for each dose vs. placebo and 14 (95% CI 9–33) for AL pooled doses vs. placebo. AL was found to be 2.3 times more likely to result in a therapeutic response than an incident of akathisia. Effect sizes calculated using Cohen's d examining the difference between PANSS total score for AL vs. placebo at Days 8, 15, 22, 29, 57 and 85 paralleled the magnitude of the effect sizes seen with NNT for PANSS response; pooling the two doses of AL, the Cohen's d for the PANSS total score change vs. placebo at Day 85 was 0.61 (95% CI 0.44-0.79), representing a moderate effect size and comparable to the NNT of 4 observed for responders defined by a ≥ 20% reduction in PANSS total score from baseline to endpoint.

Conclusions: Using the metrics of NNT and NNH, the efficacy and safety results for the pivotal study of aripiprazole lauroxil were consistent with prior aripiprazole clinical trials for the treatment of patients with an acute exacerbation of schizophrenia (e.g., oral aripiprazole or aripiprazole monohydrate as tested in acute schizophrenia trials as enumerated in their respective product labels). NNT and NNH can be used to illustrate clinically relevant outcomes in clinical trials. LHH can explicitly quantify the trade-offs that are at the core of medical decision-making. A major limitation of NNT and NNH is that these metrics are limited to binary outcomes and thus some precision is lost when dichotomizing continuous data; however, the magnitude of the NNT effect sizes for PANSS response did parallel those observed using Cohen's d when examining change in PANSS total score. In general, when re-analyzing clinical trial data using the metrics of NNT and NNH, care must be taken in the selection of appropriate thresholds for assessing medication response. Likewise, NNH calculations should focus on those relevant tolerability outcomes that are more likely to impact patient safety and future long-term adherence.

Keywords: Aripiprazole Lauroxil, Schizophrenia, Number Needed to Treat, Number Needed to Harm, Likelihood to be Helped or Harmed

Disclosure: Acadia, Alkermes, Allergan, Forum, Indivior, Intra-Cellular Therapeutics, Janssen, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva, Vanda, Consultant, Acadia, Alkermes, Allergan, Janssen, Lundbeck, Merck, Neurocrine, Otsuka, Pfizer, Shire, Sunovion, Takeda, Vanda, Honoraria, Stocks in (small number of shares of common stock): Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer purchased > 10 years ago, Stock / Equity, Wiley (Editor-in-Chief, International Journal of Clinical Practice), UpToDate (reviewer), Springer Healthcare (book), Royalties

W187. Safety, Pharmacokinetics, and Pharmacodynamics of TAK-831, a Selective D-Amino Acid Oxidase Inhibitor, in Healthy Volunteers

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Background: D-amino acid oxidase (DAAO) is the main catabolic enzyme that degrades D-serine, and it is highly expressed in glia and neurons within the mammalian brain. D-serine is a co-agonist of N-methyl-D-aspartate (NMDA) glutamate receptors, which serve several functions, including synaptic plasticity. Inhibition of DAAO increases levels of D-serine and other D-amino acids metabolized by the enzyme. TAK-831 is a highly selective and potent inhibitor of DAAO that is being developed for the treatment of Friedreich's ataxia and as an adjunctive therapy for cognitive impairment and negative symptoms of schizophrenia. The objective of these phase 1 studies was to determine the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple oral doses of TAK-831 when administered at escalating dose levels in healthy subjects.

Methods: Two phase 1 clinical trials (NCT02566759 and NCT03224325) were conducted. The first study consisted of single-rising dose (SRD) cohorts and multiple-rising dose (MRD) cohorts in a randomized, double-blind (subjects and investigators), placebo-controlled design to evaluate the safety, tolerability, PK, and PD (D- and L- serine levels) of TAK-831 in healthy subjects. Subjects were randomized using a 3:1 ratio of active:placebo in both studies. In each of the SRD cohorts in the first trial, a single dose of TAK-831 oral suspension (10, 30, 100, 250, 500, and 750 mg) or matching placebo was administered on Day 1 (fasting conditions) followed by 96 h of safety, tolerability, PK, and PD assessments. In the MRD cohorts, a single dose of TAK-831 oral suspension (30, 100, 200, or 400 mg) or matching placebo was administered on Day 1 (fasting conditions) followed by approximately 72 h of safety, tolerability, PK, and PD assessments. The once-daily dosing (QD) began on Day 4 and continued through Day 16 (13 days). There was a minimum period of 7 days between cohorts to allow for review of safety, tolerability, and PK data. Safety was assessed by adverse event (AE) monitoring, clinical laboratory tests, and physical examinations.

The second trial was conducted to continue evaluation of safety, tolerability, PK, and PD of TAK-831 in the similar SRD/MRD design to doses higher than those achieved in the first study. The

highest doses of 1200 mg in suspension and 600 mg in tablet form were included to assess TAK-831 exposure and PD levels in both cerebrospinal fluid (CSF) and plasma.

Results: All doses of TAK-831 were well tolerated. Nausea and headaches were more commonly observed in subjects taking TAK-831, and AEs were mild to moderate in intensity. There was no apparent dose-response relationship in overall incidence or for specific AEs in the SRD or MRD cohorts. There were no severe or serious AEs, and no clinically meaningful trends in vital signs, ECG parameters, or safety laboratory assessments were observed with TAK-831 administration.

TAK-831 was absorbed rapidly following SRD or MRD administrations of suspension or tablet formulation under fasting conditions. TAK-831 plasma concentrations generally reached maximal levels within median 0.25 to 2 h after dosing. Mean Cmax ranged from 90.7 to 2309 ng/mL following single doses ranging from 10 to 1200 mg, and from 165 to 3015 ng/mL following QD doses ranging from 15 to 1200 mg. Mean overall drug exposure during the dosing interval (AUC24) ranged from 271 to 10,501 h*ng/mL for QD doses of 15 to 1200 mg.

TAK-831 systemic exposures showed dose-dependent increases after single and multiple dosing. Observed inter-individual variability was low to moderate with the coefficient of variation < 50% for both Cmax and AUC. The mean terminal half-life of TAK-831 ranged from 6 to 23 h, which is consistent with the observation that the accumulation of TAK-831 was minimal after daily dosing. The CSF PK profile was in parallel with the plasma PK profile. The mean estimated CSF to plasma concentration ratio of Cmax and AUC24 fell in the range of 0.62% to 1.72%, which is similar to the free fraction of TAK-831 in plasma.

A dose-dependent increase in both plasma and CSF D-serine was observed following SRD/MRD doses of TAK-831. In plasma, the AUC24 of D-serine at steady state increased from 16.7% to 43.5% above baseline from 15 mg to 1200 mg daily doses. The magnitude of D-serine increase in CSF was higher than in plasma. The AUC24 of D-serine at steady state increased from 62.6% to 164.6% from 15 mg to 800 mg oral suspension. The D-serine elevation appeared to reach a maximum effect in both plasma and CSF when the daily dose of TAK-831 was 600 mg or above. Notably, in both plasma and CSF, the elevation in D-serine was sustained over 24 h after single doses, and the elevation persisted over the entire 24-h dosing interval after QD dosing, suggestive of a prolonged PD effect.

Conclusions: TAK-831 was safe and well tolerated in SRD/MRD doses studied in healthy subjects at oral doses up to1200 mg. Both SRD and MRD dosing regimens showed dose-dependent increases in the mean observed Cmax and AUC. Plasma and CSF D-serine levels increased in a dose-dependent manner as well, up to a plateau at ≥ 600 mg QD, demonstrating target central engagement of TAK-831 in humans. The identified PK and PD relationship provides valuable guidance for dose selection in phase 2 trials.

Keywords: D-serine, D-amino Acid Oxidase, Pharmacokinetic and Pharmacodynamic, Schizophrenia Novel Treatment

Disclosure: Takeda, Employee

W188. Prefrontal-Parietal Network Reflects Cognitive Control Demand in Monkeys Performing a Task That Measures Deficits in Schizophrenia

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Background: The ability to hold a goal or rule in working memory to direct later behavioral responses is the crux of cognitive control. Goal and rules are stored as patterns of neural activity in prefrontal cortex with the dorsolateral prefrontal cortex being activated in rule-based tasks. Research suggests that cognitive control involves not only prefrontal cortex but also prefrontal networks including the prefrontal-parietal network. Schizophrenia patients demonstrate reproducible deficits on cognitive control tasks. The goal of the current study was to advance the understanding of the relationship between cognitive control and the prefrontal-parietal network, as understanding how neural dynamics under normal conditions may be the first step to understand how computations are disrupted in the disease state. Here we trained monkeys to perform a task that has previously demonstrated cognitive control deficits in schizophrenia patients and recorded network activity in the prefrontal-parietal network during task performance.

Methods: Two male rhesus macaques were trained to perform the Dot Pattern Expectancy (DPX) task (cognitive control task). In the DPX task, two dot patterns are presented each trial separated in time (requiring working memory) and there is one dot pattern sequence that is considered the "target" sequence while all other sequences are considered "nontarget". As most trials are the "target" sequence, habitual responding patterns develop requiring cognitive control to override them. We performed large scale simultaneous neural recordings in dorsolateral prefrontal and posterior parietal cortex during task performance using microelectrodes driven through the dura into the cortical areas of interest. We evaluated neuronal preference to stimuli and response by ANCOVAs. To evaluate the strength of the relationship between neural activity and task variables as a function of time in the trial, we conducted sliding window regressions (100 ms window with 20 ms steps). We used population decoding analysis to quantify the population representation of stimuli and response as a function of time in the trial. Finally, we conducted a transmission analysis (analogous to Granger causality) to patterns of activity in ensembles of simultaneously recorded prefrontal and parietal neurons in order to evaluate the flux of task-defined signals between neurons in the separate cortical areas.

Results: In prefrontal cortex (area 9 and 46), we recorded the activity of a total of 806 neurons, in 42 neural ensembles each containing an average of 19 neurons. In posterior parietal cortex (area 7a), we recorded the activity of 416 neurons, in 25 ensembles each containing an average of 16 neurons. 84% of the neurons in each cortical area had stimuli or response specific active ($p < 0.05$ by ANCOVA). The most common task related signal in both cortical areas (90% in prefrontal, 93% in parietal) were found in neurons with significant modulation of firing rate in relation to the first stimulus in the sequence (the cue). Basic patterns of population activity were observed in both cortical areas however firing rates were higher in parietal cortex than prefrontal. The decoding and regression analyses both demonstrated that the prefrontal representation of the cue was stronger at later time points in the trial than the parietal representation. After the initial neural response to the stimuli, the recruitment curves for neuronal activity diverged such that there was faster pace of recruitment in parietal cortex (e.g. for cue, KS test, $n = 180$ parietal and prefrontal neurons, $p = 0.016$). The transmission analysis revealed a complex patent of time-varying signal coupling between the cortical areas that varied as a function of cognitive control demand.

Conclusions: The results demonstrate the distributed nature of information processing in the prefrontal-parietal network during DPX task performance. Later cue-based activity in prefrontal cortex provides evidence to suggest that prefrontal cortex plays a stronger role in computing the response based on the stimuli combination compared to parietal cortex. Earlier stimuli signals in parietal cortex is consist with a forward pass of visually evoked stimulus signals from parietal to prefrontal cortex. The network level observations we made during task performance on a task that measures cognitive control deficits in schizophrenia patients

we hope will have translational utility when attempting to understand network disruption in the disease state.

Keywords: Cognitive Control, Non-Human Primate, Prefrontal Cortex

Disclosure: Nothing to disclose.

W189. Early Auditory Information Processing in Schizophrenia as a Therapeutic Target: Preliminary Dose-Response Findings With Amphetamine

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Background: Auditory information processing (AIP) is impaired in schizophrenia (SZ) patients, as assessed in a variety of automatic neurophysiological measures of AIP and performance-based tests of sound/word detection and discrimination. Several early AIP measures have been identified as strong predictors and mediators of neurocognition and global function in SZ. We are exploring the use of AIP measures as "targets" that beneficial effects on auditory targeted cognitive training (TCT), based on responses to an acute drug challenge. Our current investigation examines the effects of the pro-attentional drug, amphetamine, on: 1) performance of a sound sweeps frequency discrimination task that is a component of a TCT suite; 2) measures of auditory "fidelity" or signal-to-noise ratio (SNR), based on a patient's ability to extract words or sentences from low-to-high levels of interfering background noise (Words-in-Noise (WIN) or Quick Speech in Noise (QuickSIN), respectively); and 3) neurophysiological measures of early AIP, including Mismatch Negativity (MMN), P3a (latency and magnitude) and prepulse inhibition of startle (PPI). Here, we report preliminary findings from an ongoing dose- and time course study of amphetamine (AMPH) effects on AIP in SZ patients.

Methods: In an ongoing study of drug dose- and time-course effects, carefully characterized SZ patients ($n = 18$; M:F = 10:8; mean age 39.5 y (24-54)) were tested on 5 days, with 1 week between each test. Test day 1 was drug-free; test days 2-5 began with a pill of placebo (PBO), 2.5, 5 or 10 mg of d-amphetamine in a double-blind, balanced order design. Testing included measures of neurocognition (MATRICS Comprehensive Cognitive Battery (MCCB)), WIN, QuickSIN, auditory event-related potentials (MMN, P3a amplitude and latency) and PPI; 210 min post-pill, subjects were also tested in a "Sound Sweeps" task that quantified an auditory "sweep discrimination threshold" (SDT) based on the ability to discriminate frequency sweep directions of paired stimuli before and after a 1-hour training session. For some measures, drug-free data was acquired from healthy subjects (HS: $n = 10$; M:F = 5:5, mean age 41.7 y (21-53)). Analyses focused on the relationships between measures of SNR performance, neurocognition, early AIP and SDT; time-course studies are ongoing.

Results: SZ patients exhibited expected deficits in neurocognition (e.g. MCCB: $F = 11.52$, $p < 0.004$) and specific early AIP measures (e.g. medium-to-large effect size deficits in MMN and P3a amplitude), compared to HS. Attention scores (MCCB A/V domain) were associated with performance in some functional / cognitive measures of SNR (e.g. QuickSIN: $r = 0.58$, $p < 0.02$) but not in more "automatic" early AIP measures (e.g. MMN: $r = -0.32$, NS). SDT performance deteriorated with repeated testing ($F = 7.25$, $p < 0.016$); this deterioration was evident after PBO ($p < 0.017$) but not after any active AMPH dose (all NS). When patients were divided based on low vs. high A/V scores, both the SDT deterioration after PBO, and the gains after AMPH, reflected large effect size changes in low A/V patients. AMPH-induced gains in SNR performance also were most evident in low vs. high A/V patients (e.g. QuickSIN: $F = 5.28$, $p < 0.04$); similar A/V-dependent AMPH-induced gains were evident in measures of PPI (60 ms) but not MMN or P3a amplitude or latency.

Conclusions: Auditory information processing deficits in SZ patients are detected in performance-based test of auditory fidelity (SNR) and frequency discrimination (SDT), and in automatic measures of early AIP, including MMN and PPI. Here we report that some but not all of these auditory processing deficits are significantly associated with attentional capacity, and that in those specific measures, deficits among attentionally-impaired SZ patients appear to be amphetamine-sensitive. These findings advance our understanding of the potential positive impact of pro-attentional interventions on auditory information processing – and conceivably auditory training components of TCT – in SZ patients.

Keywords: Schizophrenia, Information Processing, Attention, Amphetamine, Target Engagement

Disclosure: Nothing to disclose.

W190. Computational Analyses of Reinforcement Learning and Decision Making Across the Schizophrenia Spectrum

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Background: Motivational deficits are a debilitating aspect of psychotic illness, associated with impairments in real-world functioning. Cognitive neuroscience analyses of learning and motivation have begun to delineate the subprocesses of reinforcement learning (RL) and decision making (DM) and their associated neural substrates. Computational and neuroimaging investigations in people with chronic schizophrenia have indicated that motivational deficits in these patients are linked to deficits in aspects of RL such as the ability to perform rapid, working-memory-driven reinforcement learning and attenuated reward-related signals in the ventral striatum. Our goal was to investigate whether the neurocognitive correlates of motivational deficits are the same across the schizophrenia spectrum. That is, we sought to determine whether we would see the same RL deficits in unaffected first-degree relatives (FDRs) of schizophrenia patients and adolescents and young adults at clinical high risk (CHRs) for psychotic illness as we saw in individuals with a diagnosis of schizophrenia or schizoaffective disorder.

Methods: We administered probabilistic reinforcement learning paradigms, in conjunction with fMRI scanning, to samples of individuals with a diagnosis of schizophrenia or schizoaffective disorder (collectively called "SZ"; $N = 29$), FDRs of SZ patients ($N = 26$), and CHR youth ($N = 12$), along with healthy adults ($N = 36$) and adolescents ($N = 19$). In one paradigm, individuals had to determine the "better" stimulus from each of three pairs of stimuli, with the more favorable outcome occurring on 70% of choices. In one case the better outcome was a win (vs. no win), in one case the better outcome was the avoidance of a loss (vs. a loss), and in one case the better outcome was a smiley face (vs. a frown). We used computational RL models to estimate learning rates on a subject-wise basis and expected value and prediction error valence and magnitude on a trial-wise basis. We then used trial-wise estimates of expected value and reward prediction error

(RPE) valence and magnitude to construct regressors for fMRI data analysis.

Results: In these samples, we found that FDRs of SZ patients and CHR youth show many of the same RL deficits as SZ patients, to a lesser degree. When compared with healthy adults, FDRs of SZ patients showed reduced learning rates for positive RPEs [$t(54) = 2.029$, $p = 0.050$], and a trend toward lower win-stay rates [$t(54) = 1.770$, $p = 0.085$]. Relative to healthy adolescents, CHR youth showed attenuated reward-related signals in the ventrolateral striatum (-21, 5, 9; $p < 0.05$, whole-brain-corrected). These findings were consistent with prior observations that subsets of both FDRs of schizophrenia patients and youth at CHR for psychotic illness exhibit RL deficits that systematically relate to clinical ratings for motivational deficits.

Conclusions: These findings indicate that deficits in reinforcement learning factor into impairments in motivation and goal-directed behavior in both first-degree relatives of schizophrenia patients, and adolescents and young adults at clinical high risk for psychotic illness. These results support the idea that clinically-ratable motivational deficits can be tied to specific aspects of RL across the spectrum of psychotic illness.

Keywords: Reinforcement Learning, Reward, Motivation, Negative Symptoms, Computational Psychiatry

Disclosure: Nothing to disclose.

W191. Disruptions in Alpha and Theta Oscillations are Associated With Working Memory Deficits in People With Schizophrenia

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Background: People with schizophrenia (SZ) have marked deficits in working memory (WM) that contribute to impairments in other cognitive domains and relate to poor functional outcomes. Previous brain and behavior research utilized fMRI to link WM to functioning of fronto-parietal cognitive control networks and demonstrated that WM impairments in SZ are accompanied by dysfunction in these same cognitive control networks. More recently, electrophysiological (EEG) studies in nonhuman primates (Reinhart et al., 2012), suggested that coordinated low-frequency neural oscillations contribute to WM maintenance in these same brain regions. The goal of this study was to utilize EEG to examine the impact of SZ on low-frequency oscillations during WM maintenance and its association with WM deficits (Hsieh et al., 2011).

Methods: EEG data were acquired on 28 people with schizophrenia (SZ) and 47 demographically matched healthy controls (HC) using a 64-channel Neuroscan SynAmps-2 system while participants performed the Temporal Order and Item WM task (Hsieh et al., 2011). During WM trials, participants viewed 4 sequential fractal images and, after a 3000 ms delay, were presented with either two previous images and asked to indicate which was more recent (order task) or were presented with one new and one old item and asked to indicate which was previously studied (item task). Perceptual characteristics of task stimuli were selected to equate task difficulty. Time-frequency analysis focused on delay periods for correct trials only. Oscillatory power was computed by convolving single-trial epochs from each scalp electrode with six cycle complex Morlet wavelets, the results of which were binned into two frequency bands (theta, 5-7 Hz; alpha, 9-12 Hz). Data were averaged across all electrodes for each frequency band and task condition. To examine relationships between WM deficits and disruptions in alpha and theta oscillations, participants were divided into high and low performance subgroups for each of the task conditions.

Results: WM performance was less accurate (percent correct) [$F(1,73) = 33.15$, $p < .001$] in patients with SZ relative to HC across both temporal order and item WM tasks. Performance was also less accurate during the order condition than during the item condition [$F(1,73) = 33.81$, $p < .001$], with no group by task interactions [$F(1,73) = 2.99$, ns]. As predicted, SZ patients showed reduced EEG power relative to HC in both theta-band [$F(1,73) = 47.04$, $p < .001$] and alpha-band frequencies [$F(1,73) = 40.45$, $p < .001$]. For HC, theta-band activity during the order task was greater for high performing than for low performing subgroups [$t(45) = 2.44$, $p < .05$]. However, this association between theta-band activity and performance was not observed on the item task [$t(45) = .117$, ns]. Conversely, alpha-band activity in HC was greater for high performing than low performing subgroups during the item condition [$t(45) = 2.19$, $p < .05$], but not during the order condition [$t(45) = .591$, ns]. Surprisingly, SZ patients showed an inverse pattern. Theta-band activity was greater for low performing subgroups on the order task [$t(45) = 2.06$, $p < .05$], and did not differentiate performance subgroups on the item task [$t(45) = .59$, ns]. Alpha-band activity in SZ did not differentiate high and low performing subgroups for either the order task [$t(45) = .73$, ns], or the item task [$t(45) = .91$, $p < .05$].

Conclusions: Results suggest that reduced low-frequency EEG oscillations during WM maintenance are a candidate mechanism for impaired task performance in people with SZ. Specifically, the reduction in theta oscillations might be associated with deficits in the maintenance of temporal order, whereas reduced alpha band activity might be associated with deficits in maintenance of object information in WM.

Keywords: EEG/ERP Electrophysiology, Theta, Working Memory

Disclosure: Nothing to disclose.

W192. The Pharmacogenomics of Clozapine-Induced Myocarditis (PROCLAIM) Consortium

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Background: Clozapine is one of the most effective antipsychotics for treatment resistant schizophrenia and options beyond clozapine are rather limited for this disabling condition. Its use is carefully monitored due to its association with agranulocytosis, however other serious and potentially fatal cardiac side effects such as myocarditis are under-appreciated despite their association with increased risk of death. Unfortunately, our ability to identify those at greatest risk for clozapine-associated myocarditis prior to drug exposure is poor. In response to this important knowledge gap, the pharmacogenetics of clozapine-induced myocarditis (PROCLAIM) consortium was created in early 2017. The aims of the PROCLAIM consortium are to (1) unite investigators around the world to uncover genomic markers that could be used preemptively by clinicians to identify those patients at highest risk for myocarditis from clozapine therapy and (2) identify the mechanism by which clozapine induces myocardial inflammation and damage.

Methods: Prospective and retrospective recruitment of adult treatment-resistant schizophrenia patients aged 18-65 with and without a history of clozapine-induced myocarditis is on-going at

eight participating sites and will continue over the next five years. All consenting patients are asked to provide blood/saliva samples for DNA isolation, which will be used for whole genome sequencing. In a subset of participants, an additional blood sample will be used for the generation of induced pluripotent stem cells (iPSCs), which will then be differentiated into cardiomyocytes and used for in vitro functional studies to identify abnormal cellular pathways and responses.

Results: To date, 33 treatment-resistant schizophrenia individuals with a history of clozapine-induced myocarditis and 50 without a history have been recruited. Details related to recruitment rates at participating sites and inclusion/exclusion criteria as well as preliminary results of whole-genome sequencing of the first 50 participants (25 cases and 25 demographically-matched controls) and patient iPSCs will be presented as available.

Conclusions: The PROCLAIM consortium is an innovative initiative to uncover clinically-useful genomic markers of risk and determine the biological mechanisms underlying this severe adverse event. We invite all clinicians and investigators who have cared for or studied individuals who have developed myocarditis following clozapine exposure to join the PROCLAIM Consortium.

Keywords: Drug Side Effects, Whole Genome Sequencing, Induced Pluripotent Stem Cells (iPSCs)

Disclosure: Nothing to disclose.

W193. Antipsychotic-Induced Perturbations of Whole-Body Insulin Sensitivity May Occur via Inactivation of Hypothalamic K-ATP Channels

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Background: Antipsychotics are the cornerstone of treatment for schizophrenia and are widely prescribed on- and off- label for other mental illnesses. Use of these medications is, however, associated with excessive weight gain (over 75% of youth will gain > 7% body weight) and increased risk of type 2 diabetes. Recent work suggests that antipsychotic medications can immediately and independently of weight gain induce insulin resistance, and that this may occur via the central nervous system (CNS). To this point, we recently published data demonstrating that olanzapine, a highly effective and widely prescribed antipsychotic, abolishes the seminal ability of a CNS insulin infusion to restrain glucose production by the liver in rodents. These data demonstrate that olanzapine inhibits CNS insulin action, but the mechanism is unknown. The ATP-sensitive potassium (KATP) channel is a key metabolic sensor downstream of CNS insulin and nutrient signaling in the hypothalamus, which is involved the maintenance of energy and glucose homeostasis (across rodents and humans). In the present study, we set out to determine whether olanzapine in rodents inhibits KATP channel activation to disrupt peripheral glucose metabolism.

Methods: Male, Sprague Dawley rats underwent intracerbroventricular (ICV) cannulae implantation into the 3rd ventricle, and following a 1-week recovery, underwent jugular and carotid cannulation surgeries. Gold standard pancreatic euglycemic clamps were then used to measure glucose-kinetics in free running animals. During the clamp procedure, endogenous insulin secretion is inhibited by a somatostatin infusion, and insulin is replaced at basal levels. Glucose is infused at a variable rate, and the glucose infusion rate necessary to maintain euglycemia is a measure of whole-body insulin sensitivity. Prior to the clamp, rats were also pre-treated with an acute subcutaneous injection of olanzapine (OLA) or vehicle (VEH). Olanzapine dose (3 mg/kg) was based on abolishment of CNS-insulin mediated suppression of glucose production during a similar pancreatic euglycemic clamp procedure, and therapeutically relevant brain D2 occupancies (65%). A primed, continuous intracerbroventricular (ICV) infusion of the KATP channel activator Diazoxide (DIAZ) or vehicle (VEH) was administered throughout the clamp procedure. Dosing of ICV-DIAZ (total of 1.5 nmol) was based on literature demonstrating increases in whole-body insulin sensitivity during pancreatic euglycemic clamps. Based on our published lack of effects of OLA alone (i.e. in absence of a central energy stimulus) on glucose kinetics during a pancreatic clamp, VEH-VEH and OLA-VEH groups were pooled into a single control group. Groups included (central-peripheral): VEH-VEH/VEH-OLA (controls) ($n = 8$); DIAZ-VEH ($n = 10$); DIAZ-OLA ($n = 5$).

Results: The glucose infusion rate needed to maintain euglycemia during the clamp, a measure of whole body insulin sensitivity, was significantly higher in DIA-VEH rats compared to VEH-VEH/ VEH-OLA controls (2.58 mg/kg/min +/- 0.96) ($p = 0.0009$), while DIA-OLA (5.65 mg/kg/min +/- 1.08) rats had a significantly decreased glucose infusion rate compared to DIA-VEH (12.20 mg/kg/min +/- 2.11) ($p = 0.0254$). In summary, OLA co-treatment with DIAZ prevented the well-established effect of central KATP activation to increase whole-body insulin sensitivity.

Conclusions: These data suggest that olanzapine may be acting via hypothalamic KATP channel inhibition to perturb whole body insulin sensitivity. Inactivation of KATP channels (a key central metabolic sensor) may uncover a novel mechanism by which antipsychotics induce diabetes and disrupt energy homeostasis. Given the role of KATP channels, which may extend to CNS interactions of neurotransmitter systems (i.e. dopamine, glutamate), our findings may have future implications beyond adverse metabolic side-effects of these drugs to effects on psychopathology.

Keywords: Antipsychotics, Insulin Resistance, Central Nervous System, Potassium ATP Channels, Schizophrenia

Disclosure: Nothing to disclose.

W194. From Association to Function: Impaired Stress Perception in Transgenic Mice That Under-Express the Schizophrenia-Associated, Neurodevelopmental Gene, Ahi1

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Background: The Abelson helper integration site 1 (Ahi1) gene is closely implicated in ciliary function and plays a key role in brain development. Studies from our group and others have shown that Ahi1 is associated with genetic susceptibility to schizophrenia (e.g. Amman-Zalcenstein et al. Eur J Hum Genet 2006; Ingason et al. Hum Mol Genet 2010). Translational research in genetically modified mice may reveal the neurobiological mechanisms of such associations. Previous studies by our group of mice heterozygous for Ahi1 knockout (Ahi1 +/−) showed reduced brain expression of Ahi1 protein and revealed strikingly attenuated anxiety responses on several different paradigms. This was observed in the context of a normal glucocorticoid response to caffeine and pentylenetetrazole (Lotan et al Mol Psychiatry 2014, 2016). Resting-state fMRI showed decreased amygdalar connectivity with various limbic brain regions and altered network topology. However, it was not clear from previous studies whether stress-hyporesponsiveness reflected resilience or, conversely, a cognitive-emotional deficit. The present studies were designed to investigate the response of Ahi1 +/−mice to chronic

unpredictable stress (CUS) applied over 8 weeks. We hypothesized that CUS would induce anhedonia in Ahi1 + / + mice with alterations in neurogenesis, whereas Ahi1 + /- mice that were previously characterized as stress hypo-responsive, would be less affected or even indifferent to the CUS protocol from, both a behavioral and neurobiological perspective.

Methods: Ahi1 + /- mice and Ahi1 + / + littermates were generated from a colony maintained by us at the the Hebrew University, Jerusalem. All experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Male mice aged 12 weeks were assigned to 4 genotype and CUS exposure groups (Ahi1 + / + control, Ahi1 + / + CUS, Ahi1 + /- control, Ahi1 + /- CUS, 17-24 mice per group) and were exposed a CUS protocol for 8 weeks. During the last 3 weeks the mice underwent a battery of behavioral and cognitive tests with the stress protocol ongoing. Tests were recorded and analyzed using the Ethovision 10 system. Neurogenesis was evaluated in the hippocampal dentate gyrus by doublecortin staining. Corticosterone levels were measured in serum obtained from mice at sacrifice. Data were analyzed by two-way analysis of variance (ANOVA), with repeated measures when appropriate, followed by univariate tests of simple main effects.

Results: CUS exposure resulted in decreased sucrose preference of Ahi1 + / + mice but had no effect on Ahi1 + /- mice ($F[1,22] = 7.563$, $p = 0.012$, $p < 0.05$ post hoc). Consistent with our previous observations (Lotan et al., 2014, 2016), Ahi1 + /- control mice spent significantly more time in the center of the open field arena compared to Ahi1 + / + controls. CUS increased the amount of time Ahi1 + / + mice spent in the center of the arena but had no effect on Ahi1 + /- mice ($p < 0.01$). Similar results were obtained for anxiety measures on the elevated plus maze and light dark box ($p < 0.05$); hyperthermic response to acute stress ($p < 0.05$); and contextual fear conditioning ($p < 0.01$). Furthermore, CUS increased neurogenesis in Ahi1 + / + mice but had no effect on Ahi1 + /- mice ($p < 0.05$). CUS induced elevation of serum corticosterone in Ahi1 + / + mice compared to Ahi1 + / + controls but had no such effect in Ahi1 + /- mice. Overall, Ahi1 + /- mice were indifferent to the effects of CUS while their wild type (Ahi1 + / +) littermates were consistently and significantly affected.

Conclusions: Our findings suggest that Ahi1 under-expression during neurodevelopment, as manifested by Ahi1 + /−mice, impairs perception of fear-inducing stimuli in these mice and renders them stress hyporesponsive. Ahi1 deficiency may attenuate the perception and/or integration of environmental stressors as a result of impaired corticolimbic connectivity or aberrant functional wiring. Abnormalities related to the processing of fear-inducing stimuli have been demonstrated in patients with schizophrenia and have been associated with abnormalities of amygdala connectivity (Mukherjee et al, Schiz Res 2011). Thus, the findings reported here for mice that under-express Ahi1 provide heuristic clues as to the functional role this gene in schizophrenia.

Keywords: Schizophrenia Genetics, Animal Model, Chronic Stress

Disclosure: Taliaz Health, Advisory Board, Trendlines, Consultant

W195. Schizotypal Personality Disorder as a Model of Genetic Risk for Schizophrenia: Evidence From Polygenic Risk Scores

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Background: Schizotypal personality disorder (SPD) is a non-psychotic schizophrenia (SZ)-spectrum disorder that shares milder forms of the clinical and cognitive symptoms of SZ, and many of its biological correlates. However, knowledge of the genetic architecture of SPD is very limited, and while SPD and SZ co-occur in families, the extent of overlap between SPD and SZ genetic risk is unknown.

We aimed to compare SPD and healthy controls (HC) using polygenic risk scores (PRS) derived from Psychiatric Genomics Consortium (PGC) genome-wide association studies (GWAS) of SZ.

Methods: Fifty SPD patients and 67 healthy controls were rigorously diagnosed with structured interviews and genotyped on the Illumina OmniExpress. Polygenic risk scores (PRS) were derived from QC-positive SNPs intersected with the Psychiatric Genomics Consortium SZ genome-wide association studies (GWAS) and pruned for linkage disequilibrium $r2 < 0.1$ (86,268 SNPs). The PGC GWAS samples contained 35,476 case and 46,839 control samples of mostly European and < 10% east Asian ancestry (Schizophrenia Working Group of the PGC, 2014) and an African descent sample GWAS of 6152 cases and 3198 controls (PGC, unpublished).

Logistic regression: Covariates included age, sex, 8 of the top 20 genotype-derived principal components associated with diagnosis, and number of missing SNPs. We focused on the $p < 0.01$ PRS for the PGC GWAS and all SNPs PRS for the African descent GWAS since they have the highest association with SZ case/control status in their respective discovery GWAS samples.

Results: After QC $n = 101$ with 709,923 SNPs, a PRS based on 7,294 SNPs with Psychiatric Genomics Consortium (PGC) SZ GWAS $p < 0.01$ was significantly positively associated with SPD versus controls in Non-African-descent patients ($R2 = 0.11$, $p = 0.0104$), with a similar variance explained as the PRS in SZ samples in the PGC. For the African descent GWAS PRS, the results were significant, but the effect size was lower ($R2 = 0.03$, $p = 0.047$).

Conclusions: Our results support the historical notion of SPD as a disorder that shares some of the genetic liability for SZ. Understanding the genetic underpinnings of SPD may shed light on risk and protective factors against overt psychosis. Moreover, PRS can be used to selectively recruit SPD patients who are genetically closest to SZ, as SPD is an ideal model of SZ that is free from confounds such as chronic antipsychotic medication use and global disability.

Keywords: Schizotypy, Schizotypal Personality Disorder, Schizophrenia, GWAS, Polygenic Risk Score

Disclosure: Neurocrine Bioscience, Inc, Grant, AI Cure, LLC, Grant

W196. Neurobiological Roots of Schizophrenia

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Background: The estimated heritability of schizophrenia is 80–85%, and if one of monozygotic twins has the illness, the risk for the other twin is about 50%. It has remained unclear which

factors are associated just with the increased risk, and which neurobiological mechanisms are related to the cascade leading to actual onset of illness. It has also remained a mystery why this neurodevelopmental disorder manifests itself after adolescence.

Methods: We used iPSC-derived neurons from 5 monozygotic twin pairs discordant for schizophrenia (3 female and 2 male pairs; all 5 affected individuals were chronically symptomatic and treated with antipsychotics, 3 with clozapine) and 6 healthy controls matched by age and sex to enhance signal by minimizing genetic heterogeneity. Diagnoses were assigned using DSM-IV criteria and SCID-I interviews, and severity of symptoms was assessed with PANSS. Skin biopsy-derived fibroblasts were reprogrammed into integration-free induced pluripotent stem cell (iPSCs) lines by Sendai virus technology. The cells were further differentiated into cortical-like neurons expressing markers of GABAergic and glutamatergic neurons. The top genes from RNAseq analysis were validated by quantitative polymerase chain reaction (qPCR). In the proteomic analysis, the 16 samples were processed through the SysQuant workflow using Tandem Mass Tag (TMT) reagents within two TMT 10plexes. A reference pool containing all samples was also included. To identify statistically significant regulated features (peptide, phosphopeptides or proteins), a LIMMA-based modified t-test was performed at the peptide, phosphopeptide and protein levels in pairwise comparisons using distribution-dependent fold change (FC) and p-value (p) thresholds.

Results: Transcriptomic and proteomic analyses showed very large effect sizes (differences up to 7.3-fold in gene expression and 2.7-fold in protein levels in the comparison between affected twin versus healthy twin). Among the most robust findings related to disease status were down-regulation of COL6A3, SSTR2, and LHX1 genes, and altered glycosaminoglycan, CAMK2G-related AMPA/NMDA/glutamate, GABAergic synapse, and purine metabolism pathways. While only 12% of genes were differentially expressed between healthy males and females, the majority of the illness-related genes were sex-specific (p-values down to 2.2 x 10E-16 for the difference). Most of the genes with the largest effect sizes were different between males and females. Neurons of affected twins with treatment-resistant illness showed markedly larger calcium responses for NMDA-specific glutamate ($p < 0.001$) and, in somewhat smaller extent, for GABA exposure than their healthy twins, and these alterations were normalized when the neurons were treated with clozapine.

Conclusions: Results imply that somatostatin 2 receptor defect may be a factor leading to dysfunction of NMDA receptors in somatostatin/calreticulin GABAergic interneurons, and that clozapine might have a beneficial effect on this cascade. Consistent findings on down-regulation of N-glygan and calnexin/calreticulin pathways, affecting protein folding in endoplastic reticulum, indicate also their major role in schizophrenia. Our results imply that although both sexes share many of the final common pathways involving the same proteins, the underlying primary pathophysiology of schizophrenia may differ between males and females. This may explain why the disease typically manifests after adolescence, when the expression levels of many sex-specific genes change.

Keywords: Schizophrenia, Induced Pluripotent Stem Cells (iPSCs), Twins, Monozygotic

Disclosure: Nothing to disclose.

W197. Complement Component 4 Variation and Clinical Characteristics of Schizophrenia

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Background: Robust evidence has emerged supporting the complement component 4 (C4) as a susceptibility gene in schizophrenia (Sekar et al. 2016). In the immune system, C4 tags pathogens for destruction by macrophages and other phagocytes. In the brain, C4 appears to tag unwanted synapses for pruning by microglia. Genetic variation of C4 is complex. There are two C4 isotypes (C4A and C4B). Each isotype exhibits copy number variation (0-5 copies), along with structural variation (long and short C4 genes) resulting from the presence or absence of a human endogenous retroviral insertion (HERV). Sekar et al. found that genetic variants conferring increased C4A expression were associated with schizophrenia, potentially increasing risk of the disease through excessive synaptic pruning. Notably, C4A copy number is a proxy for C4A expression. Here, we aim to further explore the relationship between C4 variation and clinical characteristics of schizophrenia.

Methods: We investigated the association between C4 structural variation and the following: schizophrenia case status, age of onset, and Global Assessment of Functioning (GAF). Our clinical sample comprised 680 adults with schizophrenia or schizoaffective disorder recruited at the Centre for Addiction and Mental Health (Toronto, Canada), including 375 of European ancestry. Clinical data was obtained from Structured Clinical Interviews for DSM-IIIR or DSM-IV and medical record review.

Copy numbers of C4A, C4B, long C4 genes (with HERV), and short C4 genes (without HERV) were determined using TaqMan copy number assays on an Applied Biosystems real-time PCR system following manufacturer's protocols. Resolution of structural haplotypes of C4 is in progress. C4 copy numbers (C4A, C4B, long C4 genes, short C4 genes) for 111 healthy controls genotyped by Sekar et al. were used for case-control analysis.

Descriptive and association analyses were done using R version 3.3.1 statistical software, with the rms package. Association for each C4 copy number (C4A, C4B, long C4 genes, short C4 genes) was tested by logistic regression for binary outcomes (i.e. case-control status) and linear regression for continuous outcomes (i.e. age at onset, GAF) using an additive genotypic model (C4 copy number coded numerically as 0 - 6 according to copy number). We adjusted for sex in the models of age at onset. We performed analyses in the total sample and in the European subset and used a Bonferroni-corrected significance threshold of $p < 0.05/12 = 0.004$ (3 phenotypes * 4 genotypes = 12 independent tests).

Results: We found that genomes contained 0-6 C4A genes, 0-5 C4B genes, 0-6 long C4 genes, and 0-4 short C4 genes.

There was no difference in C4A, C4B, long, or short C4 gene copy numbers between patients and controls in the total sample or the European ancestry subset of the sample ($p > 0.05$ after Bonferroni correction). Among European ancestry patients, C4A copy number was nominally associated with age of onset (0 copies: mean age at onset +/- SD = 17 years old +/- 5 years; 1-2 copies: 21 +/- 6; 3 copies: 22 +/- 5; 4 copies: 23 +/- 3; $p = 0.017$ before Bonferroni correction). No association was observed between C4B, long or short C4 gene copy numbers and age of onset, or between any C4 copy numbers and GAF among European ancestry patients ($p > 0.05$ after Bonferroni correction).

Conclusions: Sekar et al. found C4A expression strongly associated with schizophrenia in a large sample of 28,799 cases and 35,986 controls. While we were unable to replicate this finding in our sample of 680 patients and 111 controls, we did observe a

trend for association between C4A copy number and age at onset of schizophrenia. Interestingly, we observed higher C4A copy numbers among patients with age at onset during late adolescence – a time when synaptic pruning is occurring in brain regions involved in schizophrenia, such as the temporal lobe and prefrontal cortex. Limitations of our study include low statistical power, lack of structural haplotype resolution of C4, and lack of genotype-predicted C4A expression in brain. These limitations may explain the differences between our findings and those of Sekar et al. Future work is ongoing to increase sample size, obtain antipsychotic treatment response data for analysis, resolve C4 structural haplotypes, and estimate brain C4A expression based on C4 genotypes.

Keywords: Schizophrenia, Immune, Complement Component 4, Genetic Association Study

Disclosure: Nothing to disclose.

W198. Proton Magnetic Resonance Spectroscopic Imaging of Gray and White Matter in Bipolar-I and Schizophrenia Early and Late in the Illness

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Background: Glutamine plus glutamate (Glx), as well as N-acetylaspartate compounds, (NAAc), a marker of neuronal viability, are quantified with proton magnetic resonance spectroscopy (1H-MRS) and have been reported altered in psychotic disorders. However, few studies have compared these neurometabolites in bipolar disorder and schizophrenia.

Methods: Used 1H-MRS imaging from an axial supraventricular slab of gray matter (GM; medial-frontal and medial-parietal) and white matter (WM; bilateral-frontal and bilateral-parietal) voxels. Bipolar-I with history of psychosis ($N = 43$), schizophrenia ($N = 41$) and healthy controls (HC; $N = 45$) were studied.

Results: Amongst younger (age ≤ 40 years) bipolar-I vs HC subjects we found increased Glx in WM ($p < 0.001$), with NAAc reductions in WM ($p < 0.001$) and lower NAAc ($p < 0.001$) and myo-inositol in GM ($p = 0.002$). Amongst older bipolar-I (vs. HC) in WM regions we found reductions in: NAAc ($p < 0.001$), total-choline ($p < 0.001$), total-creatine ($p < 0.001$) and myo-inositol ($p < 0.001$); in GM only Glx was increased ($p < 0.005$). Contrasts between bipolar-I and schizophrenia produced fewer results: amongst younger subjects, reduced NAAc ($p < 0.001$) in WM and lower myo-inositol in GM ($p = 0.04$) in bipolar-I vs. schizophrenia. In the older patients, schizophrenia had higher GM NAAc ($p = 0.009$) than bipolar-I.

Conclusions: Though both disorders have increased Glx and reduced NAAc, suggestive of neuronal dysfunction, the timing and location of the abnormalities may differ between the two.

Keywords: Disorders of glutamate, N-acetylaspartate, Psychotic Disorders

Disclosure: Nothing to disclose.

W199. Body and Brain Imaging Correlates of Antipsychotic (AP)-Induced Glucose Dysregulation in AP-Naïve Schizophrenia Patients

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Background: Mortality rates in patients with schizophrenia are two- to three-fold higher than the general population with cardiovascular disease (CVD) identified as the main culprit. Increased authorized and off-label use of atypical antipsychotics (AAP) in children and adolescents necessitate a better understanding of the extent of their side effects in the paediatric population given their association with CVD and T2DM. Evidence supports the notion that regional distribution of body fat, rather than absolute weight, is the critical correlate of the metabolic abnormalities. Specifically, visceral adipose tissue (VAT) – the intrabdominal fat surrounding organs and blood vessels is associated with ectopic storage of lipids in undesired sites such as liver, muscle and pancreas and is a significant, independent predictor of type 2 diabetes mellitus (T2DM) and CVD. However, the effect of AAP on these measures is not well understood in medication-naïve adolescents. Furthermore, the relationship between change in visceral adipose tissue and change in brain structure is unknown. This study proposes to obtain abdominal and brain magnetic resonance images (MRI) to quantify the accumulation of hepatic and visceral fat and structural changes in the brain following first-time use of antipsychotics in adolescents. We also obtained anthropometric and laboratory metabolic indices in these patients.

Methods: Eleven patients (4 female, 7 male) with an average age = 21.4 (range = 16-29) participated in the study. Patients were recruited from the Emergency Department and/or inpatient unit for Early Psychosis. All antipsychotics were prescribed and titrated by their primary physician as required. Diagnoses included Schizophrenia (2), Other Specified Schizophrenia and Other Psychotic Disorders (6), Major Depressive Disorder (1) and Autism Spectrum Disorder. Medications included risperidone (4), paliperidone (2), lurasidone (2) and aripiprazole (2). All medications were prescribed orally. At baseline and at 12 weeks, we completed a medical history and physical examination (including height, weight and waist circumference), lipid panel (including triglycerides, total cholesterol, low-density lipoprotein and high-density lipoprotein), fasting glucose and an oral glucose tolerance test (OGTT). A 3 T MRI was used to obtain high resolution T1 image of the brain. VAT was measured using 3 axial abdominal MRI slices at the L4-L5 vertebrae level. A chemical-shift-based water-fat pulse sequence called Dixon based on a 3D spoiled gradient echo with multi-peak spectral modeling of fat and correction for T2* variations, was used to measure liver fat content. Subcortical structural volumes, adipose tissue volumes (subcutaneous and visceral components), and liver fat fraction averages are compared across time. Correlations between the imaging measures and anthropometric and biochemical measures were examined.

Results: We identified significant increases in weight ($p = 0.008$), BMI ($p = 0.007$), waist circumference ($p = 0.037$), total cholesterol ($p = 0.032$), and LDL ($p = 0.005$) when 3-month follow-up data were compared to baseline measurements. There was not a significant difference in change in liver fat or overall visceral adipose tissue. Right striatum ($p = 0.025$) and right globus pallidus ($p = 0.013$) were found to increase in size after the antipsychotic trial.

Change in weight correlated significantly with the change in waist circumference ($p = 0.03$), post-OGTT (120 mins) glucose measurement ($p = 0.007$), visceral adipose tissue ($p = 0.003$) and liver fat ($p = 0.048$). A strong correlation was observed between the change in post-OGTT (120 mins) glucose measurement and the change in liver fat ($p = 0.004$). Change in liver fat correlated with change in the volume of the right thalamus ($p = 0.03$) and right amygdala ($p = 0.01$) while change in waist circumference correlated with change in the volume of the left hippocampus ($p = 0.007$) and right globus pallidus ($p = 0.016$).

Conclusions: Our findings suggest that metabolic perturbations due to antipsychotic intake are multi-level and multi-systemic. Significant correlation between imaging, and anthropometric and

blood-based measures of metabolic health raise the possibility of using imaging techniques to predict or detect these abnormalities early. Future studies should look at low-cost imaging techniques like ultrasound to predict the onset of antipsychotic-induced metabolic abnormalities. The results also suggest a link between antipsychotic use, metabolic consequences, and brain structure and function that needs further exploration.

Keywords: Antipsychotic, Metabolic Side-Effects, MR Imaging, Visceral Obesity, Adolescent

Disclosure: Nothing to disclose.

W200. Glutathione Levels and Activities of Glutathione Metabolism Enzymes in Patients With Schizophrenia: A Systematic Review and Meta-Analysis

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Background: Accumulating evidence has suggested that oxidative stress may contribute to the pathophysiology of schizophrenia (SZ). Glutathione (GSH) is the most abundant antioxidant and it plays an important role in preventing oxidative stress. Animal studies have suggested that GSH deficits may cause SZ-like behavior by impairing parvalbumin interneurons or myelination. Further, GSH deficits may reciprocally interact with N-methyl-D-aspartate receptor (NMDAR) hypofunction and neuroinflammation, which are also considered to be associated with SZ. Previous studies have noted abnormal GSH levels in patients with SZ; however, findings are inconsistent due to differences in study characteristics. Thus, we conducted a meta-analysis to investigate whether any differences in GSH levels may exist between patients with SZ and healthy controls (HCs) in an effort to find potential abnormalities within the GSH system in patients with SZ. Moreover, we compared enzymatic activity in the GSH metabolic pathway between the two groups.

Methods: A literature search was conducted using Embase, Medline, PsycINFO, and PubMed. Original studies written in English that measured levels of GSH metabolites (GSH, GSSG, and GSH + GSSG (= total GSH [tGSH])) or activities of GSH metabolism enzymes (GCL, GS, GPx, GR, and GST) with any techniques were investigated in both patients with SZ and HCs. The variables extracted from each included study were the levels of GSH metabolites, activities of GSH metabolism enzymes, diagnoses, age, sex, antipsychotic treatment status, duration of illness (DOI), Positive and Negative Syndrome Scale (PANSS) total scores, and methods of GSH measurement. For main meta-analyses, standardized mean differences (SMDs) were calculated to determine the differences in levels of GSH metabolites between the groups, and secondary meta-analyses for activities of GSH metabolism enzymes were performed in the same manner. Subgroup analyses were performed for materials (i.e., blood, CSF, brain tissue, MRS, or fibroblast cell groups), antipsychotics status (only for unmedicated patients group), and clinical status (only for first-episode psychosis (FEP) group). Meta-regression analyses were conducted for patients' age, the proportion of antipsychotics-medicated patients, the proportion of male patients, chlorpromazine equivalent, DOI, and PANSS total scores.

Results: Out of 1273 initial records, 40 articles were included in main meta-analyses. Comparisons of GSH, GSSG, and tGSH between the two groups were reported in 34, 9, and 15 studies, respectively. Peripheral GSH levels were decreased ($n = 25$, SMD $= -1.02$, CI $= -1.37$ to -0.67, $P < 0.001$) and there was a trend towards a decrease in central GSH levels ($n = 9$, SMD $= -0.45$, CI $= -0.87$ to -0.033, $P = 0.035$) in patients with SZ in comparison to HCs. Peripheral GSSG levels did not differ between the two groups ($n = 7$, SMD $= -0.22$, CI $= -0.67$ to 0.23, $P = 0.34$). Peripheral tGSH levels were lower in patients with SZ than in HCs ($n = 12$, SMD $= -1.01$, CI $= -1.59$ to -0.42, $P = 0.001$). The significance level was set at a p-value $< 0.05/4$ analyses $= 0.013$. We could not perform meta-analyses for central GSSG and tGSH due to the small number of studies.

In secondary meta-analysis, GPx activity was lower in patients with SZ than in HCs ($n = 36$, SMD $= -0.63$, CI $= -1.01$ to -0.24, $P = 0.002$). There was no difference in GR activity between the two groups ($n = 7$, SMD $= -0.44$, CI $= -1.16$ to 0.29, $P = 0.239$). The significance level was set at a p-value $< 0.05/2$ analyses $= 0.025$. For other GSH metabolism enzymes (GCL, GS, and GST), we could not perform meta-analyses because there were less than five studies about these enzymes.

Subgroup analysis showed that blood GSH levels were lower in patients with SZ than in HCs, while GSH levels measured with 1H-MRS did not differ significantly between the two groups. In unmedicated patients with SZ, GSH levels were lower, and tGSH levels showed trend to be lower than those in HCs. There was no difference in GSH levels between patients with FEP and HCs. Meta-regression analyses showed no significant relationships among any of the SMDs of GSH, GSSG, and tGSH levels and any of the modulators.

Conclusions: Our findings of lower levels of GSH and tGSH in patients with SZ compared to HCs are consistent with existing clinical and animal studies, which indicate that GSH deficits may contribute to pathophysiology of SZ. Moreover, decreased activity of GPx suggests abnormalities in the GSH redox cycle, which could be the cause of GSH deficits. Subgroup analyses showed that decreased GSH levels may exist in patients with SZ even before antipsychotic administration, while no differences were found between patients with FEP and HCs, which may be attributable to the fact that FEP includes other type of psychotic illnesses. Given the relatively small sample sizes for included studies and the small number of studies examining factors such as enzyme activity in GSH synthesis, further studies with a much larger sample size are needed to elucidate the abnormalities of the entire GSH system in SZ.

Keywords: Schizophrenia, Glutathione (GSH), GSSG, tGSH

Disclosure: Nothing to disclose.

W201. Striatal Glutamate, Subcortical Structure and Clinical Response to First-Line Treatment in First-Episode Psychosis Patients

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Background: Glutamate levels in the precommissural dorsal-caudate are increased in first-episode psychosis patients (FEP). We investigated whether clinical response is related to striatal glutamate levels, surface area and volumetric structure.

Methods: Proton magnetic resonance spectroscopy and T1-weighted images were used to measure glutamate levels and volumetric of the dorsal caudate in 48 antipsychotic-naive FEP patients. After 4 weeks of treatment with risperidone, clinical response was rated (defined as a reduction of at least 40% in the positive subscale of the PANSS), and patients underwent a second MR study. Glutamate levels were estimated using LCModel and

corrected for the cerebrospinal fluid (CSF) proportion within the voxel. Fully-automated segmentation of striatal subdivisions was carried out using the Multiple Automatically Generated Templates (MAGeT-Brain) algorithm.

Results: After treatment, 29 patients responded to treatment and 19 did not. The proportions of voxel grey matter, white matter and CFS did not differ among groups at baseline nor in post-treatment scans. At baseline scan, the non-responder group showed trend-level glutamate elevations compared to responders ($p = 0.07$) and had significantly larger right striatal volumes than treatment responders ($t = 2.135$, $p = 0.04$); At 4 weeks, non-responders showed higher levels of glutamate compared to responders ($p = 0.02$). Moreover, there were no group differences in FWHM values or signal-to noise ratios in either time points. Associations between left striatum surface area and glutamate were different for responders and non-responders at baseline (glutamate main effect significant at 20%FDR); increased glutamate levels were associated with smaller surface area for responders, but there was no association for non-responders in the dorsal caudate. Striatal volume increased in both responders and non-responders from pre- to post-treatment timepoints (main effect of time for left striatum $t = 2.68$, $p = 0.01$ and right striatum $t = 2.316$, $p = 0.03$). At the post-treatment timepoint; a significant effect of glutamate was observed in the right striatal surface area (precommissural head of caudate); again, increased glutamate levels were associated with smaller surface area in responders, and no surface difference in non-responders (< 10%FDR).

Conclusions: Our results support that striatal glutamate levels and structure differ in FEP patients that do not respond to first-line treatment in comparison to responders. In addition, our results suggest that baseline striatal glutamate level could predict treatment response.

Keywords: Glutamate, First Episode Psychosis, Magnetic Resonance Imaging, Dorsal Caudate, Antipsychotic Treatment

Disclosure: Janssen, Consultant

W202. Testing the Psychotic Dysconnectivity Hypothesis in 1318 Individuals

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Background: The dysconnectivity hypothesis posits that the positive and negative symptoms observed in individuals with psychotic illnesses result from a breakdown of the integration of and communication between brain regions. The link between psychosis and connectivity was first proposed by Wernicke in 1906, who suggested that psychotic disorders arise from pathology of the brain's association fibers. Today, abnormal connectivity between brain regions is considered central to the pathophysiology of psychosis, and is supported by evidence from neuron structure, white-matter tractography, electrophysiological coherence, and resting state functional MRI connectivity. While each of these levels of measurement provide insights into the pathobiology of psychotic disorders, recent advances in multivariate network and graph-theoretical methods have increased the popularity of resting state MRI-based connectivity experiments. Many of these studies utilize a "seed" approach to examine group differences in connection strength or correlation from a specific neuroanatomic area or seed (e.g. dorsolateral prefrontal cortex, thalamus, posterior cingulate). Unfortunately, seed-based approaches require investigators to choose, a priori, a region believed to be differentially associated with psychosis. Given that multiple seed regions appear to have aberrant connectivity patterns in psychosis and given that the exact anatomic location chosen is often not contrasted with nearby regions, it is likely that seed-based functional connectivity analyses do not fully quantify the dysconnectivity observed in the illness. In contrast, whole-brain functional connectivity measures putatively index the totality of psychotic dysconnectivity. A recent meta-analysis reported that individuals with schizophrenia, the prototypical psychotic illness, exhibit significant decreases in measures of local organization and small-worldness in whole brain, without evidence for disruption in global communication. Unfortunately, there is little consistency across whole-brain studies regarding the exact neuroanatomic network implicated, with studies reporting particularly pronounced dysconnectivity in sensory, cerebellar, cingulo-opercular, salience, fronto-parietal, default mode or data-defined networks. Inconsistent findings likely reflect small sample sizes and the complexity and flexibility of the various analytic pipelines. Despite this lack of neuroanatomic specificity, a pattern of results from whole-brain functional connectivity studies using global network measures has emerged whereby individuals with psychotic illnesses have less clustered but equally or more distributed topology, implying a 'subtle randomization' of whole-brain functional network organization.

Combining network connectivity approaches with machine learning methods, such as support vector machine (SVM) learning, multiple investigators have successfully classified individuals into diagnostic groups with accuracies ranging from 59 to 95%. However, these methods are necessarily sample and method dependent and larger samples typically result in poorer classification accuracy. Thus, examining multiple large data sets analyzed with identical methods is necessary to document the potential utility of whole brain resting state connectivity as a potential biomarker for psychotic disorders.

Methods: The goal of the present experiment is to provide such data by applying the identical surface-based whole-brain connectivity pipeline and SVM analysis to four large independent samples including a total of 557 individuals with psychosis and 761 controls. More specifically, after a comprehensive quality control process, we used the Human Connectome Project pipeline to preprocess data and parcellated each subject's time-series data into the regions represented in the Gordon atlas along with subcortical and cerebellar regions. These parcels were combined into a set of 15 functionally defined networks and normalized time courses were correlated with all other networks (with and without controlling for GSR). The resulting correlation matrices were included in SVM analyses.

Results: The first sample (120 patients/224 controls) resulted in a 70% accuracy for classifying subjects by diagnosis. Analysis for the remaining three data sets is ongoing. We will conduct SVM analyses (both linear and non-liner variants) independently for each sample (sample sizes 344, 228, 596, and 150 respectively) and combining samples for different magnets and sites into a single large analysis.

Conclusions: Although we anticipate classification accuracy to be well below that required for accurate diagnoses, these data provide support for the dysconnectivity hypothesis and for the use of whole-brain resting state connectivity to measure it. At the same time, the moderate classification accuracy suggests that resting fMRI measures of connectivity are not sufficient to serve as robust biomarkers for psychotic illness.

Keywords: Functional Connectivity, Psychotic Disorders, Machine Learning Classification

Disclosure: Nothing to disclose.

W203. Heterogeneity of Brain Structure Alterations in Patients With Never-Treated First Episode Schizophrenia

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Background: Schizophrenia is a heterogeneous clinical syndrome. Several recent studies have used cluster analysis to delineate discrete homogenous subgroups of patients within psychiatric disorders. The diverse data obtained from modern MRI neuroanatomic studies may provide the basis for resolving neurobiological heterogeneity within schizophrenia. We studied a large sample of antipsychotic-naïve first-episode schizophrenia (FES) patients to identify patient subgroups based on gray matter features and compared this clustering with that in a sample of chronic treated patients.

Methods: High resolution 3D T1 structural MRI data were acquired from 163 FES patients and 163 controls, and chronic treated patients from the B-SNIP study (133 patients and 133 controls). Three major anatomical features (cortical thickness, surface area and cortical volume) were extracted. Concatenating 68 regions*3 neuroantomical features for each subject, a 204 x N matrix was generated. We employed principal component analysis to obtain each principal component and the corresponding eigenvalues. Using Matlab function "pdist" with Mahalanobis distance, we obtained a NxN dissimilarity matrix for a cluster analysis. A density peak-based clustering algorithm was employed to intuitively classify schizophrenia patients into subtypes with distinct neuroanatomical patterns. The topological properties of gray matter connectivity were also analyzed among the different subtypes. All imaging features were compared between subtypes and controls, and the clinical outcome at one year follow up in the FES group was also analyzed.

Results: We found three subtypes of neuroanatomic alterations in the FES sample. Subtype one showed increased cortical surface area and volume especially in lateral orbitofrontal cortex, fusiform and precentral gyri. Subtype two showed increased cortical thickness and volume including orbitofrontal and lateral occipital cortex. Subtype three showed decreased cortical area and volume including cuneus and precentral cortex. The topological properties of gray matter connectivity were also different among the 3 subgroups. Although subgroups did not differ in baseline symptoms, subtype 2 patients showed poorer clinical outcome relative to the other two groups ($p < .05$). Statistically significant similarities and differences of clustering features between FES and BSNIP data were also found and will be discussed.

Conclusions: We show three novel and clinically relevant subtypes of schizophrenia patients with distinct patterns of regional structural alterations and topological properties at illness onset prior to treatment. The subtype with increased cortical thickness and volume at a drug-naïve state showed poorer clinical outcome.

Keywords: Antipsychotic-Naïve First-Episode Schizophrenia, Brain, Structural MRI, Cluster Analysis

Disclosure: Nothing to disclose.

W204. White Matter Abnormalities in Never-Treated Patients With Long-Term Schizophrenia

Abstract not included.

W205. Baseline Behavioral and Frontoparietal Cognitive Control Related BOLD Activity Predicts Clinical Improvement During Early Psychosis Specialty Care at One Year Follow-Up in Recent Onset Psychosis

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Background: Response to treatment in psychotic disorders is highly variable, and biomarkers of treatment response have been lacking to date. As a result, trial and error remains the basis for care in early psychosis and poor outcomes continue to be common in individuals, even when duration of untreated psychosis is relatively short and specialized clinical care is provided. Early identification of patients who are less likely to have good treatment responses would help identify individuals who would benefit from alternative and/or supplemental interventions. Here we evaluated the ability of behavioral and functional magnetic resonance imaging (fMRI)-based measures of cognitive control related brain activity collected during initial engagement in treatment to predict symptomatic improvement in early psychosis patients after one year.

Methods: Patients with either schizophrenia ($n = 67$, 50 M/17 F, mean age 20.7 years) or Type I bipolar disorder with psychotic features ($n = 17$, 9 M/8 F, mean age 21.2 years) were scanned during the AX CPT task at the beginning of treatment and re-evaluated clinically after 12 months of early psychosis specialty care. Patients were classified as Improvers (> 20% improvement on Brief Psychiatric Rating Scale (BPRS) Total Score at one-year follow-up vs. baseline) or Non-Improvers. Improvers and Non-Improvers were compared on functional and behavioral (d-prime context) measures of cognitive control at baseline. Cognitive control measures were also combined into a single principle component score which was then evaluated for its ability to predict BPRS improvement after controlling for baseline BPRS using logistic regression.

Results: Compared to Non-Improvers, Improvers showed significantly higher activation of the dorsolateral prefrontal ($t = 2.43$, $p = 0.02$) and superior parietal ($t = 2.93$, $p = 0.004$) cortices during proactive cognitive control. D-prime context and duration of untreated psychosis did not significantly differ between groups, while responders had increased baseline total BPRS scores ($p < 0.001$). Relative to an initial model with only baseline BPRS as a predictor, adding the cognitive control principal component improved logistic regression model fit (step chi-square = 6.0, $p = 0.01$), as well as improved classification accuracy (67% vs. 73%), specificity (58% vs. 63%), sensitivity (74% vs. 80%), positive predictive value (68% vs. 73%), and negative predictive value (65% vs. 73%).

Conclusions: These results suggest that fMRI data collected at baseline can predict symptomatic clinical improvement after one year in psychosis, and that dysfunctional cognitive control processes may contribute to treatment response in psychotic disorders. They further suggest the potential utility of cognitive control as a biomarker for treatment responsiveness in early psychosis and the potential for using fMRI as a personalized medicine tool in future clinical care. They also highlight the need for additional mechanistic studies to identify the pathophysiological mechanisms underlying impaired cognitive control-related functional circuitry in early psychosis.

Keywords: Treatment-Response, Functional MRI (fMRI), Cognitive Control

Disclosure: Nothing to disclose.

W206. Patterns of Cortical Brain Measures and Cognition in Antipsychotic-Naïve First-Episode Schizophrenia Patients: A Partial Least Squares Correlation Analysis

Abstract not included.

W207. Striatal Volume and Functional Connectivity Predict Weight Gain in Early-Phase Psychosis

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Background: Second-generation antipsychotic drugs (SGAs) are essential in the treatment of psychotic disorders but are well-known for inducing substantial weight gain and obesity. Critically, weight gain may reduce life expectancy for up to 20-30 years in patients with psychotic disorders, and prognostic bio-markers are generally lacking. The dorsal striatum, rich in dopamine D2 receptors which are antagonized by antipsychotic medications, plays a key role in the human reward system and in appetite regulation, suggesting that altered dopamine activity in the striatal reward circuitry may be responsible for increased food craving and resultant weight gain.

Methods: Here, we measured striatal volume and striatal resting state functional connectivity at baseline, and weight gain over the course of 12 weeks of antipsychotic treatment in 81 patients with early-phase psychosis. We also included a sample of 58 healthy controls. Weight measurements were completed at baseline, and then weekly for 4 weeks, and every 2 weeks until week 12. We used linear mixed models to compute individual weight gain trajectories. Striatal volume and whole-brain striatal connectivity were then calculated for each subject and used to assess the relationship between striatal structure and function and individual weight gain in multiple regression models.

Results: Patients had similar baseline weights and body mass indices (BMI) compared to healthy controls. There was no evidence that prior drug exposure or duration of untreated psychosis correlated with baseline BMI. Higher left putamen volume and lower frontopolar connectivity predicted magnitude of weight gain in patients, and these effects multiplied when the structure-function interaction was considered.

Conclusions: These results provide evidence for a synergistic effect of striatal structure and function on antipsychotics-induced weight gain. Lower fronto-striatal connectivity, implicated in less optimal long-term decision making, was associated with more weight gain, and this relationship was stronger for higher compared to lower left putamen volumes.

Keywords: Metabolic Side Effects, Antipsychotic Treatment, Neuroimaging Biomarkers, Early Psychosis

Disclosure: Nothing to disclose.

W208. Novel PET Probe to Visualize AMPA Receptors in Living Human Brain

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Background: Glutamatergic synapses play central roles in almost all of neuronal functions such as learning, motor and sensory functions. Among glutamate receptors, AMPARs are the "actual mediator" at glutamatergic synapses. Since the cloning of AMPARs approximately two decades ago, enormous number of papers have reported the importance of AMPARs on neuronal functions including diseases. Despite the accumulation of knowledge of physiological roles of AMPARs, its clinical translation is limited. Main reason for this is that we are not able to visualize AMPARs in living human brain. The development of positron emission tomography (PET) probe for AMPAR could be a powerful tool to tackle this problem. Thus, a PET probe to visualize AMPAR in living human brain is an "unmet medical needs" for the development of drugs acting to AMPAR.

Methods: We developed a novel PET probe for AMPARs. We radio-labelled a derivative of 4-[2-(phenylsulfonylamino) ethylthio]-2,6-difuluoro-phenoxyacetamide with 11 C, named [11 C]K-2. First, its specific binding to AMPARs was examined in rodents. In a subsequent cross-sectional study, male healthy participants aged 30-49 ($n = 8$) and patients aged 30-49 with mesial temporal lobe epilepsy ($n = 3$), depression ($n = 10$), and schizophrenia ($n = 10$), respectively, underwent a [11 C]K-2 PET scan and received clinical assessments for symptomatology. For those with epilepsy, correlation between AMPAR-PET-signals and protein amount of AMPARs with surgically removed tissue was calculated.

Results: We detected specific PET signals of AMPAR in rat and human. We successfully visualized the accumulation of PET signals of AMPAR in the temporal lobe of the hemisphere with epileptic foci where the 99mECD-SPECT blood flow signal was lower compared to the contralateral hemisphere. Further, we detected significant positive correlation between AMPAR-PET-signals and protein amount of AMPARs with surgically removed tissue from epileptic patients. Further, [11 C]K-2 revealed systemic reduction of AMPARs in patients with depression, while patients with schizophrenia exhibited focal decrease of AMPARs in parahippocampal and cingulate gyrus. These decreases were significantly correlated with symptomatology scores measured with the Mongomery-Asberg Depression Rating Scale for depression and the Positive and Negative Syndrome Scale for schizophrenia.

Conclusions: Thus, [11 C]K-2 is a potent PET tracer for AMPAR providing biological basis of neuropsychiatric disorders.

Keywords: AMPA Receptors, PET Probe, Psychiatric Disorders

Disclosure: Nothing to disclose.

W209. Glutamatergic Neurometabolite Levels in Patients With Ultra Treatment-Resistant Schizophrenia: A Cross-Sectional 3 T Proton MRS Study

Abstract not included.

W210. Reward Processing as a Vulnerability Indicator for Psychosis: Results From a Twin Study

Abstract not included.

W211. Aerobic Exercise Induces a Robust and Sustained Restoration of Cognitive Function in the Sub-Chronic

Phencyclidine Animal Model for Cognitive Impairment in Schizophrenia

Jo Neill, Antonio Gonzalez, Lisa Heaney, Matthew Burgess, Toby Aarons, Giovanni Podda, Ben Grayson, Syeda Munni, Michael Harte, Tom Metcalf*

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Background: Cognitive deficits in schizophrenia remain an unmet clinical need and have a significant impact on outcome and quality of life for patients and carers (Keefe & Harvey, 2012. In: Novel Antischizophrenia Treatments (pp. 11-37). Springer, Berlin, Heidelberg). Clinical studies are emerging to demonstrate efficacy of supervised exercise on cognitive function in schizophrenia patients (Firth et al. 2017 Schizophrenia Bulletin, 43(3), 546-556). Exercise increases hippocampal and plasma levels of brain-derived neurotrophic factor (BDNF), a growth factor protein that modulates long-term potentiation (Berchtold et al., 2005 Neuroscience, 133(3), 853-861). BDNF is integral for cognitive performance in the short-term, and is involved in neurodevelopment, synaptic regulation, and synaptic plasticity, as these processes are dysregulated in schizophrenia, it is hypothesised that BDNF is also implicated in the pathology of the disorder (Nieto et al, 2013 Frontiers in Psychiatry, 4, 45). The sub-chronic phencyclidine (scPCP) rat model and novel object recognition (NOR) task have been well validated for relevance to schizophrenia in our laboratory and elsewhere (Grayson et al. 2015 Behavioural Brain Research, 285, 176-193; Cadinu et al. 2017 Neuropharmacology, https://doi.org/10.1016/j.neuropharm). Our aim is to investigate sustainability of the effects of aerobic exercise on cognitive function in schizophrenia using a well validated animal model and to explore mechanisms by which aerobic exercise reverses cognitive deficits, with a focus on BDNF. A further aim is to determine whether changes in serum BDNF correlate with brain changes supporting a non-invasive biomarker approach in patients.

Methods: Four groups of adult female Lister Hooded rats ($n = 15$ per group) were used: vehicle control, vehicle exercise, scPCP control, and scPCP exercise. Rats were treated with either saline ($N = 30$) or PCP (2 mg/kg i.p. $N = 30$) twice a day for 7 days, followed by 7 days washout and then given access to running wheels in individual cages for 1 h a day, 5 times a week, for 6 weeks. Control groups had access to immobilised running wheels. The NOR task (with a 1-minute inter-trial interval) was conducted immediately pre-exercise, post-exercise, 2 weeks post-exercise, and 4 weeks post-exercise. For BDNF analysis, 5 rats from each group were sacrificed at each time point, resulting in 10 rats per group for the 2 weeks post-exercise NOR testing and 5 for the 4 weeks' testing. Serum and brain (pre-frontal cortex and hippocampus) BDNF levels were analysed by ELISA and high throughput western blotting using WES. Data were analysed by ANOVA and post-hoc student's t-test.

Results: Pre-exercise vehicle, but not the scPCP group, successfully discriminated the novel from familiar object ($P < 0.001$; $n = 30$ in the scPCP group and 30 in the vehicle group). Immediately post-exercise, all groups successfully discriminated the novel from familiar object ($P < 0.001$) apart from the scPCP no exercise group. At 2 weeks post-exercise, again, all groups successfully discriminated novel from familiar object ($P < 0.01$) again apart from the scPCP no exercise group. At 4 weeks post-exercise both vehicle groups discriminated novel from familiar object ($P < 0.05$ vehicle control group and $P < 0.01$ vehicle exercise group), the scPCP no exercise group were still impaired and the scPCP exercise group showed some ability to discriminate between the objects but this effect failed to achieve statistical significance ($P = 0.079$). BDNF data is currently being processed and will be presented at the meeting.

Conclusions: This work demonstrates that 6 weeks of aerobic exercise, 1 h per day 5 days a week produces a robust and sustained reversal of cognitive deficits in a well validated pharmacological rat model of relevance to schizophrenia. Our work to evaluate potential mechanisms of this effect through BDNF in serum and brain could inform future therapeutic strategies in patients.

Keywords: Aerobic Exercise, NMDA Antagonists, Animal Models, BDNF, Cognition

Disclosure: Lundbeck, Consultant, Otsuka, Consultant, Autifony, Advisory Board

W212. Human Monocyte-Derived-Neuronal-Like Cells (MDNCs) Structurally Resemble Human Developing Neurons After Five Days in Culture

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Background: Postmortem studies of neurodevelopmental disorders such as schizophrenia and autism have consistently shown deficits in neuronal structure. However, postmortem analyses do not allow researchers to assess dynamic neurostructural changes. The advent of induced pluripotent stem cells (IPSCs) has opened this possibility. But IPSCs (just as any other model) have limitations such as eliciting genetic and epigenetic abnormalities, lack of reproducibility with samples from the same individual as well as being costly and time consuming.

Methods: We have developed a protocol to transdifferentiate blood circulating monocytes into neuronal-like cells in only 20 days and without reprograming the cells' genome. Instead, we utilize different growth factors, antioxidants and conditioned media. This model is a practical, inexpensive and noninvasive approach to obtain neuronal-like cells directly from patients.

Results: We have transdifferentiated monocytes into neuronal-like cells from over 70 individuals and established that transdifferentiated neuronal-like cells express several neuronal markers and present spontaneous action potentials as well as postsynaptic inhibitory and excitatory currents. Moreover, transdifferentiation of monocytes delivers reproducible results in sequential samples from the same donors. We have also determined that when these neuronal-like cells are exposed to either dopamine or colchicine, they respond similarly to neurons by retracting their neuronal arborizations. In addition, we have recently evidenced that monocyte-derived-neuronal-like cells (MDNCs) structurally resemble human developing neurons (HDN) after five days in culture as well as human SH-SY5Y neuroblastoma cells differentiated with retinoic acid. Five structural parameters were used for this comparison; primary neurite length, secondary neurite length as well as number of primary, secondary and tertiary neurites per cell. The length of secondary neurites was practically the same between the three cell types (21 ± 0.7 µm for MDNCs, 21.5 ± 1 µm for SH-SY5Y and 18.6 ± 2 µm for HDN, mean ± SEM). Primary neurite length was comparable between the three cell types but there were statistical differences. Human developing neurons had longer primary neurites (99 ± 3.8 µm, mean ± SEM) than the other two cell types and neuroblastoma cells had the shortest (93 ± 1.7 µm for MDNCs and 76 ± 1.8 µm for SH-SY5Y, mean ± SEM). Number of primary (5 ± 0.1, mean ± SEM) and secondary neurites (9 ± 0.4, mean ± SEM) was significantly higher in transdifferentiated neuronal-like cells, while SH-SY5Y had the lowest number of primary neurites (3.7 ± 0.2 for HDN and 3.6 ± 0.1 for SH-SY5Y,

mean ± SEM) and human developing neurons had the lowest number of secondary neurites (2.8 ± 0.2 for SH-SY5Y and 1 ± 0.1 for HDN, mean ± SEM). The number of tertiary neurites was also significantly higher in MDNCs (1.3 ± 0.1 mean ± SEM) while human neurons had the lowest number (0.5 ± 0.1 for SH-SY5Y and 0.04 ± 0.02 for HDN, mean ± SEM). Of note, if cultured for a longer time, human neurons continue to extend neuronal processes and their arborizations become more complex, whereas neuroblastoma cells and MDNCs remain stable. (MDNCs n = 350, SH-SY5Y n = 234 and HDN n = 83).

Conclusions: Human circulating monocytes can be consistently transdifferentiated into neuronal-like cells in only 20 days and without reprograming. Furthermore, MDNCs structurally resemble human neurons after five days in culture and thus, allow researchers to study dynamic neurostructural changes directly in cells from patients with neurodevelopmental disorders such as schizophrenia and autism.

Keywords: Adult Stem Cells, Transdifferentiation, Neurodevelopmental Disorders, Induced Pluripotent Stem Cells (iPSCs)

Disclosure: Nothing to disclose.

W213. Recovery in First Episode Psychosis: Domain Specific Measurement of Health, Home, Purpose and Community

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Background: Recovery is an evolving concept in modern mental health treatment that incorporates outcomes beyond improvement in symptoms and reduction in adverse consequences such as hospitalizations. There are numerous definitions of recovery. The US Substance Abuse and Mental Health Services Administration (SAMHSA) defines recovery as incorporating four domains; Health, Home, Purpose and Community. We wished to explore the SAMHSA four-domain concept with a Confirmatory Factor Analysis (CFA).

Methods: Data used were from the RAISE-ETP study that included 404 participants with first-episode non-affective psychosis at 34 sites. Measures identified that indexed that recovery were assessed for six-month intervals over two years. In the domains of Health, Purpose and Community there were measures that incorporated sub-measures. For example, under Health we had both symptom factors and a remission measure that incorporated two of the factors. We pruned the indices to ensure that no individual item was included more than once. In the Health domain, there were 18 measures. The following eight were included in the CFA; Positive and Negative Syndrome Scale symptom remission, Calgary Depression Scale absence of depression, absence of substance abuse, suicidal intent, psychiatric hospitalization, medical hospitalization, SF-12 mental health and SF-12 physical health. For Home there was only one measure, stable home. For Purpose there were 14 measures. The following four were included; instrumental role as worker or student; Quality of Life Scale (QLS) role performance, QLS intrapsychic foundations, and financial independence. For Community there were eight measures; the following three were included; QLS social network, self-rated overall emotional health and self-rated overall life satisfaction. A four- factor model following the four domains of Health, Home, Purpose and Community was tested using Confirmatory Factor Analysis (CFA) using measures collected at all time points. The model fit was evaluated using following statistics: the Chi-square being non-significant (> .05), and absolute and incremental fit indices (the comparative fit index Goodness of Fit Index (CFI) and the Root Mean Square Error of Approximation (RMSEA) < .08, (GFI) = > .90 and (Standardized) Root Mean Square Residual (SRMR) < .08. The Goodness-of-Fit Index (GFI) is an alternative to the $\chi 2$ test and measures how close the fit of the hypothesized model is to the observed covariance matrix. The Root Mean Square Error of Approximation (RMSEA) is an absolute non-centrality-based index. RMSEA values range from zero to one with a smaller RMSEA indicating better model fit. By convention, the higher GFI and lower $\chi 2$, RMSEA, values indicate better fit.

Results: The CFA included 1174 observations. An observation represented a subject who had all 16 measures at a given time-point. Fit to the model was not confirmed by any of the four accepted standard measures. $\chi 2$ (102) = 2161.02; p < .001, GFI = .82, RMSEA = .13 and SRMR = .15. Those values did not indicate a good fit between the model and the observed data. Inspection of the correlation matrix among variables revealed moderate (> .25 p < .01) correlations across the domains. Symptom Remission, an indicator of Health was correlated with Role Performance and Intrapsychic Foundations all indicators of Purpose. Role Performance was correlated with Social Networks, an indicator of Community. The highest correlations were between the SF-12 measure of mental health and global life satisfaction r = .51 and self rated emotional health (.50).

Conclusions: The results of this CFA fail to confirm a factor structure that corresponds to the specific domains of recovery as defined by SAMHSA using a broad array of measures that tap these domains drawn from assessments conducted by clinicians and self-report. Further analyses can address a number of questions. Do the more granular measures included in the study better reflect these recovery domains? For example, specific psychopathology symptom factors may be more precisely related to Health. Self reported specific measures of stigma, well-being and hope may better index Community than the global measures included here. Are there alternative definitions of recovery domains that are a better fit to the data? Is the factor structure of recovery different in multi-episode patients than in this first-episode cohort? Correlations of measures across domains suggest that there is interdependence among them. Thus, assessment of recovery that cuts across domains may be a useful step in the study of the course and treatment for patients with first episode psychosis.

Keywords: First Episode Psychosis, Assessment, Recovery Definition, Factor Analysis

Disclosure: Nothing to disclose.

W214. Suicidal and Aggressive Behaviors and Risk Factors in a Large Schizophrenia Sample (n = 626)

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Background: Rates of completed suicide and suicide attempts are high in people with schizophrenia and in those developing the disorder. These individuals are also more likely than those in the general population to behave aggressively towards others. However, there are few large, broadly-phenotyped samples available for comprehensive testing of associations of key markers – such as suicide attempts or assaultive behavior – with clinical, demographic and behavioral risk factors reported in the literature, including mood disorder, antisocial characteristics, reported suicidal ideation, verbal assaults or threats of violence, non-

suicidal self-injury, destructive behavior, cognitive abilities, diagnostic subtypes, age of onset, and other factors. To our knowledge, suicide attempts and assaultive behaviors also have not been tested for association with polygenic risk for schizophrenia, cognition and educational attainment.

Methods: Comprehensive demographic, clinical, behavioral, cognitive, and personality phenotyping was completed for participants in a NIMH study of schizophrenia. Participants also provided blood for genotyping. Historical medical records (e.g., from prior hospitalizations) were obtained for most participants. We abstracted and coded information about suicidal and aggressive behaviors, and a wide range of risk factors, from a detailed review of the complete NIMH study participation files of 626 people with schizophrenia or schizoaffective disorder. We used standard procedures to extract DNA and obtained genotypes using Illumina Bead Chips (510K-2.5 M SNP chips). To test for genetic associations at a cumulative level, we used available GWAS summary statistics and standard methodology to construct sets of polygenic scores (PGS) in our sample for schizophrenia genetic risk, cognition genetics, and educational attainment genetics. Analyses determined the prevalence of documented suicide ideation and attempts, non-suicidal self-injury, and destructive and assaultive behaviors. Regression analyses tested the associations of risk factors with documented suicide attempt history and physical assault history. Ordered, sequential regression analyses were used to adjust for relevant covariates and to tease apart the unique contributions of different predictors.

Results: In data on suicidal and aggressive behaviors, abstracted from detailed medical records of 626 clinically stable participants in a large NIMH schizophrenia study, suicidal and aggressive behaviors were quite common. Records revealed suicidal ideation in 73.5% of participants, non-suicidal self-injury in 29.4%, and a suicidal attempt history in 43.1%. The lethality of suicide attempts was generally low to moderate. Past destructive behavior (involving inanimate objects) was documented for 32.7% of the sample and verbal assault or threat was documented for 42.7%. A history of physical violence was noted in files for 32.7%. Most instances of physical assaults were rated as mild to moderate and were directed at family members and other individuals known to the participant. Analyses highlighted some risk factors that showed similar effects for individuals with documented suicidal and aggressive behaviors (e.g., prodromal age; for suicide $p = 8.9E-07$, $r2 = .051$; for aggression $p = .007$, $r2 = .016$), others that were more specific to one or the other behavior category (e.g., non-suicidal self-injury for suicide, $p = 2.4E-07$, $r2 = .055$; destructive behavior, $p = 5.0E-06$, $r2 = .042$, and education, $p = .003$, $r2 = .019$, for aggression), and some with diverging effects for suicidal versus aggressive behaviors (e.g., sex, age). For example, women in our schizophrenia sample were more likely than men to have had a documented suicide attempt ($p = .005$, $r2 = .017$) and women who were older at the time of study participation were more likely to have an attempt history than women who were younger ($p = .027$, $r2 = .034$). In contrast, men were more likely than women to have a documented physical assault history ($p = 6.5E-04$, $r2 = .026$), and men who were younger when they participated were more likely to have assaulted others than older male participants ($p = .008$, $r2 = .022$). In regard to genetics, a documented history of suicide attempt was not related to PGS for schizophrenia, cognition or educational attainment. In contrast, across inclusive p-value scoring thresholds (i.e., $pT = .05$ to $pT = 1.0$), PGS for cognition were significantly lower in individuals with a documented history of physical assault, and directionally consistent with the finding for years of education, although effect sizes were small (e.g., at $pT = 1.0$, $p = .028$, $r2 = .011$). The same pattern was evident for educational attainment, although the difference was not statistically reliable. There was no relationship between assault history and schizophrenia risk genetics.

Conclusions: A documented history of suicidal and/or aggressive behaviors, including suicide attempts and physical assault, was very common in a large, clinically stable sample of people with schizophrenia or schizoaffective disorder. Different risk factors for suicidal vs. aggressive behaviors showed interesting patterns of convergence, divergence and separation, although effects sizes were modest. Analyses suggested a small but significant influence of cognition genetics on propensity for physical assault.

Keywords: Suicidal Behavior, Aggressive Behavior, Schizophrenia, Risk Factors, Polygenic Scores

Disclosure: Nothing to disclose.

W215. Clinical Profiles and Conversion Rates Among Young Individuals With Autism Spectrum Disorder Who Present to Clinical High Risk for Psychosis Services

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Background: The overlap versus independence of autism spectrum disorder (ASD) and schizophrenia has been a historically contentious topic. Although high rates of psychotic symptoms have been identified in individuals with ASD, the nature, prevalence, and prognostic significance of subclinical psychotic experiences in ASD remain poorly understood.

Methods: This study sought to compare baseline characteristics, clinical profiles, and conversion outcomes between young individuals at clinical high risk for psychosis (CHR) who presented with a prior ASD diagnosis during the second phase of the North American Prodrome Longitudinal Study (NAPLS, $n = 764$).

Results: Our results revealed that CHR patients with ASD (CHR/ASD+, $n = 26$) tended to exhibit greater social (GF:Social; $\beta = -.16$, $t = -4.44$, $p < 0.001$, Cohen's $d = 0.89$) and social cognitive difficulties ($t = -3.17$, $p = 0.002$), but expressed relatively similar levels of core psychosis symptoms relative to non-ASD CHR (CHR/ASD-) patients. Risk for conversion to co-occurring psychosis (18.2% CHR/ASD+ versus 16.8% CHR/ASD-; Log-rank $\chi2(1) = 0.21$, $p = 0.65$)) was equivalent between CHR/ASD+ and CHR/ASD- individuals, and the NAPLS2 Psychosis Risk Calculator predicted conversion to co-occurring psychosis equally well across groups. Across groups, there was a main effect of risk (1 yr: $\beta = 0.32$, $t = 6.96$, $p < 0.001$; 2 yr: $\beta = 0.32$, $t = 6.89$, $p < 0.001$, but no main effect of ASD status (1 yr: $\beta = 0.03$, $t = 0.74$, $p = 0.46$; 2 yr: $\beta = 0.03$, $t = 0.56$, $p = 0.58$) or risk by ASD status interaction (1 yr: $\beta = -0.02$, $t = -0.48$, $p = 0.63$; 2 yr: $\beta = -0.10$, $t = -1.31$, $p = 0.19$).

Conclusions: These results suggest that baseline psychosis symptoms, predictors of risk for conversion, and ultimate conversion rates are similar in CHR patients with and without ASD. They further suggest that ASD must not be considered a mutually exclusive diagnosis, when such youth present in CHR settings. Future research is needed to better track trajectories in larger cohorts of CHR/ASD+ individuals and to understand whether treatment recommendations effective in the broader CHR population are useful for this particular population as well.

Keywords: Clinical High-Risk State for Psychosis, Autism Spectrum Disorders, Comorbidity, Symptoms, Development

Disclosure: Nothing to disclose.

W216. Host-Parasite Interaction Associated With Major Mental Illness

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Background: Patients with major mental illness such as schizophrenia and bipolar disorder are often reported to have co-morbid physical conditions. Thus, systemic alterations affecting both brain and peripheral tissues may underlie these disorders. Although numerous studies over the last two decades reported elevated levels of anti-Toxoplasma gondii (T. gondii) antibodies in patients with major mental illnesses, the underlying biology was unclear. In this study, we have addressed the role of a major mental illness-related susceptibility factor, Disrupted in schizophrenia (DISC1), in altered host immune responses against T. gondii.

Methods: Human lymphoblastoid cells with known DISC1 genotypes were infected with T. gondii tachyzoites to examine the impact of DISC1 607 variation on immune response as measured by cell biology assay and gene expression analysis. Sera from human subjects with known DISC1 genotypes were analyzed for the presence of anti-T. gondii IgG by SNP genotyping and enzyme-linked immunosorbent assay (ELISA).

Results: Our cell culture experiments showed that cellular responses against T. gondii infection are dysregulated in the absence of functional DISC1. DISC1 was also shown to interact with activating transcription factor 4 (ATF4), a transcription factor controlling the expression of genes related to cellular stress and inflammation, via 607 Leu residue. Gene expression analysis revealed that cAMP response element (CRE)-dependent gene expression was dysregulated in human lymphoblastoid cells with DISC1 607 Phe/Phe variant upon T. gondii infection. In human populations, the DISC1 607Phe variation was specifically associated with elevated serum anti-T. gondii IgG levels in one cohort. The lack of T. gondii seropositive individuals with DISC1 607 Phe/Phe genotype in another independent cohort prevented us from conducting confirmation studies. Thus, these findings still need to be followed up by multi-institutional larger studies in the near future.

Conclusions: This study provides mechanistic insight into one of the few well-replicated serological observations in major mental illness. As shown here, factors that has been implicated in neurodevelopment and/or mental illness may be involved in host immune responses against pathogenic infections throughout the life.

Keywords: Genetic Variation, Immune Responses, Toxoplasma, DISC1

Disclosure: Nothing to disclose.

W217. Temperament Subtypes in Schizophrenia

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Background: Schizophrenia has heterogeneous presentations, treatment responses, and functional outcomes. One possible source of heterogeneity is individual differences in temperament. Inhibited temperament is the biologically-based propensity to respond to novel people and situations with caution of fear and is associated with increased risk for developing anxiety and depression. Two small studies have shown that patients with schizophrenia have higher levels of childhood inhibited temperament. In the present study, we test the hypothesis that there is a subgroup of patients that have a childhood inhibited temperament and characterize temperament subgroups on measures of anxiety, depression, psychosis symptoms, and quality of life.

Methods: Participants were patients with schizophrenia (N = 174, 66.0% male) and controls (N = 186, 58.6% male). Temperament was assessed with a validated retrospective self-report measure; participants were classified as having inhibited, average, or uninhibited temperament. Chi-square analyses tested for group differences in temperament distribution. Within the group of patients, ANOVAs tested for temperament group differences in anxiety diagnosis, anxiety symptoms, psychosis symptoms, and quality of life.

Results: A prominent subgroup of patients (33%) had a childhood inhibited temperament; this was significantly higher than the control group (5.4%). The inhibited subgroup had a higher rate of anxiety disorders, higher levels of anxiety symptoms, higher levels of negative emotional symptoms, and lower quality of life (all ps < 0.05).

Conclusions: The current study parsed the heterogeneity of patients with schizophrenia using temperament to explain variation in the social and emotional components of schizophrenia. These results suggest a possible neurodevelopmental pathway to schizophrenia characterized by temperament.

Keywords: Temperament, Schizophrenia Subtypes, Mood and Anxiety Disorders

Disclosure: Nothing to disclose.

W218. Nimodipine Decreases Frontal and Parietal Cortical Activity During Working Memory in Healthy Subjects

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Background: There are currently no medications approved to treat the cognitive deficits experienced by patients with schizophrenia. Patients with schizophrenia have increased cortical brain activity during working memory, which may be a biomarker for cognitive dysfunction. The L-type calcium channel gene, CACNA1C, is a validated risk gene for schizophrenia and the target of calcium channel blockers. Carriers of the CACNA1C risk-associated genotype (rs1006737 A allele) have increased frontal cortical activity during working memory. Carriers of this risk SNP also have higher CACNA1C mRNA expression in the dorsolateral prefrontal cortex. The goal of this study was to determine how the brain-penetrant calcium channel blocker, nimodipine, changes brain activity during working memory and other cognitive and emotional processes.

Methods: We conducted a double-blind randomized cross-over pharmacoMRI study of a single 60 mg dose of oral nimodipine solution and matching placebo solution in healthy, young, non-smoking, right-handed, Caucasian men. Subjects were prospectively genotyped for rs1006737 using a standard Taqman assay. Plasma nimodipine concentrations were measured using LCMS. The main outcome measure was brain activation measured by 3 T

BOLD fMRI, while completing cognitive and emotional tasks including the N-back working memory task, a modified monetary incentive delay task, an emotional memory task, an emotional face matching task, and the flanker cognitive control task. Functional MRI data was collected using the Siemens PACE MOCO sequence and imaging data was processed using standard methods in SPM12. The first-level contrast for the N-back task was 2-back > 0-back, and the second-level contrast was the effect of nimodipine on the 2 > 0 back contrast (thresholded at pFWE < 0.05, k = 10 voxels). To test the effect of rs1006737 genotype, we completed a linear regression (AA > GA > GG) using the difference in brain activation in the Placebo-Nimodipine contrast (thresholded at p < 0.001 uncorrected, k = 10, masked for main effect of nimodipine). Our a priori hypothesis was that nimodipine would decrease frontal cortical brain activity during the working memory task and this decrease would be greatest in carriers of the CACNA1C risk-associated genotype.

Results: Nimodipine significantly decreased frontal cortical activity by 39.1% (peak voxel T = 7.48) and parietal cortical brain activity by 42.8% (peak voxel T = 7.28) during the N-back working memory task (2-back > 0-back contrast; paired t-test, PFWE < 0.001 for peak voxels; n = 28). Higher peripheral nimodipine concentrations were correlated with a greater decrease in activation in the superior parietal cortex after nimodipine compared to placebo (p < 0.001 uncorrected, T = 4.16). Changes in brain activation were not correlated with peripheral blood pressure or heart rate. Performance was not significantly different on the 2-back between placebo (91.6% correct) and nimodipine (91.5% correct). Of the 28 subjects, 14 were carriers of rs1006737 GG, 4 carried GA, and 10 carried the AA risk-associated genotype. Carriers of the risk-associated allele, A, had a greater decrease in frontal cortical activation during working memory compared to non-risk allele carriers (p < 0.001 uncorrected, T = 4.24). No differences in brain activation were found between nimodipine and placebo for other cognitive or emotional tasks (pFWE > 0.05).

Conclusions: Nimodipine decreased frontal cortical and parietal cortical brain activation during working memory. The effects of nimodipine were selective to working memory, as no differences were found in brain activation during any other cognitive or emotional task. While cortical brain activity decreased in all genotype groups, the greatest decrease was found in those who carried the risk-associated genotype. Future studies should be conducted to test if the decreased cortical brain activity after nimodipine is associated with improved working memory performance in patients with schizophrenia, particularly those who carry the risk-associated genotype.

Keywords: Voltage-Gated Calcium Channel, CACNA1C, Functional MRI (fMRI), Working Memory, Human Genetics

Disclosure: Nothing to disclose.

W219. TAK-041 Modulates Amphetamine-Induced Dopamine Release in the Human Brain: A Phase 1 [11 C]PHNO Pet Study

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Background: TAK-041 is an orally administered small molecule agonist of the G-protein-coupled receptor 139 (GPCR139) and is currently under development for the treatment of schizophrenia. Pre-treatment of rats with TAK-041 attenuated amphetamine (AMPH)-induced dopamine release in the nucleus accumbens, as measured by microdialysis. In the human brain, the only method available to measure directly dopamine release uses positron emission tomography (PET) and selective dopamine-2 and -3 (D < sub > 2 < sub > /D < sub > 3 < sub >) receptor radioligands. Agonist radioligands, such as [< super > 11 < super > C]PHNO, have been demonstrated to be the most sensitive for detecting changes in dopamine release. We utilized a translational biomarker approach to determine TAK-041 brain penetration in healthy volunteers and demonstrated pharmacodynamic modulation of central dopaminergic pathways by blunting AMPH-induced dopamine release.

Methods: An open-label phase 1 study evaluated the effects of single oral doses of TAK-041 on AMPH-induced dopamine release utilizing PET and [11-C]PHNO. Ten healthy volunteers received 3 PET scans each: at baseline, 3 h following a single oral dose of d-AMPH (0.5 mg/kg), and at 5 h following a single oral dose of TAK-041 (with another 0.5 mg/kg dose of d-AMPH administered 2 h post-TAK-041 and 3 h before the [11-C]PHNO PET scan). Dynamic PET data were acquired on Siemens Biograph 6 scanners for 90 minutes following the intravenous injection of [11-C]PHNO. Structural brain magnetic resonance imaging (MRI) data were acquired to aid in the delineation of anatomical regions of interest. PET data were analyzed within MIAKAT < super > TM < super > , corrected for attenuation and motion, using the simplified reference tissue model with the cerebellum as the reference region, to derive regional binding potentials (BP < sub > ND < sub >). The putamen and the ventral Striatum were chosen as primary regions of interest, based on data indicating the most robust AMPH-induced reduction in [11-C]PHNO BP < sub > ND < sub > in previous studies.

The magnitude of synaptic dopamine release was assumed to be proportional to dBP < sub > ND < sub > . The percentage reduction in [11-C]PHNO BP < sub > ND < sub > from baseline following an AMPH challenge was calculated as follows: dBP < sub > ND < sub > = 100 x (1 – BP < sub > ND < sub > < super > Post-dose < super > /BP < sub > ND < sub > < super > Baseline < super >)

TAK-041-induced attenuation of dopamine release (ddBP < sub > ND < sub >) was measured as the % change in dBP < sub > ND < sub > after TAK-041 pre-treatment:

ddBP < sub > ND < sub > = 100 x (1 – dBP < sub > ND < sub > [< super > TAK-041 + AMPH < super >]/dBP < sub > ND < sub > [< super > AMPH < super >])

Results: Ten healthy volunteers completed all 3 PET scans, with 5 receiving 20 mg and 5 receiving 40 mg of TAK-041. The mean injected [11-C]PHNO activity was 121 MBq (± 26 SD), and the mean injected mass of PHNO was 1.43 μg/kg (± 0.34 SD), with the average difference in injected mass between baseline and post-dose scans being 6% (± 6 SD). Administration of AMPH alone resulted in a robust reduction of [11-C]PHNO BP < sub > ND < sub > in both putamen (mean dBP < sub > ND < sub > = 22% ± 5) and ventral striatum (mean dBP < sub > ND < sub > = 26% ± 8). Administration of TAK-041 modulated the magnitude of post-AMPH dBP < sub > ND < sub > in a dose-dependent manner in putamen (20 mg TAK-041: ddBP < sub > ND < sub > = 17% ± 11; 40 mg TAK-041: ddBP < sub > ND < sub > = 36% ± 8) and ventral striatum (20 mg TAK-041: ddBP < sub > ND < sub > = 14% ± 14; 40 mg TAK-041: ddBP < sub > ND < sub > = 23% ± 20), consistent with a reduction of extracellular dopamine release post-AMPH as seen by microdialysis in the rodent brain.

Conclusions: We demonstrated a dose-dependent modulation of human central dopaminergic pathways by the GPCR139 agonist TAK-041. This effect is consistent with previously established effects in the rodent brain. A translational biomarker strategy was implemented successfully in phase 1, demonstrating brain penetration and pharmacologic modulation of a CNS target by a drug candidate in development, and these data will inform dose selection for subsequent clinical studies with TAK-041. To our knowledge, this is the first robust demonstration of a modulation

of AMPH-induced dopamine release in the human brain by a novel drug candidate.

Keywords: PET Imaging, Amphetamine, Pharmacodynamics, Schizophrenia Novel Treatment

Disclosure: Takeda, Employee, Astellas, Employee (Spouse)

W220. Betahistine Effects on Weight-Related Measures in Patients Treated With Antipsychotic Medications: A Double Blind Placebo Controlled Study

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Background: Weight gain during treatment with antipsychotics is a prominent side-effect, especially with some second-generation antipsychotics, such as olanzapine and clozapine, and pharmacological treatments which ameliorate this side-effect are important to investigate. Decreases in histaminergic transmission in the brain induced by antipsychotics may be one of the mechanisms contributing to weight gain. Since betahistine is a histaminergic agonist, it may potentially counteract the weight gain effects of antipsychotics.

Methods: We conducted a double-blind placebo-controlled study to evaluate the effects of 12 weeks of treatment with betahistine (N = 29) or placebo (N = 22) on anthropomorphically measured weight related parameters, appetite, and fasting glucose-lipid and leptin levels in 51 patients treated with first and/or second-generation antipsychotics who had gained weight during treatment or had high body-mass-index (BMI). Psychopathology and side-effects were also assessed with relevant scales.

Results: In a sub-group of patients being treated with olanzapine or clozapine, betahistine was significantly ($P < .05$) better than placebo in decreasing or preventing increases in weight (3.1 kg difference from placebo), BMI and waist circumference. Betahistine did not decrease weight or BMI in patients treated with other antipsychotics. It did not significantly improve appetite or glucose-lipid measures in either subgroup. There were no significant differences in side-effects or psychopathology changes in the betahistine vs. placebo treated patients.

Conclusions: These results suggest that betahistine may potentially be a useful adjunctive drug for decreasing weight gain in patients treated with antipsychotics that are potent histamine antagonists, such as olanzapine or clozapine, but may not be useful as a general weight loss drug in patients on other antipsychotic medications. The results justify larger placebo-controlled studies to further confirm these effects before specific recommendations can be made for routine use.

Keywords: Betahisitine, Weight Gain, Antipsychotics, Olanzapine, Clozapine

Disclosure: Abbot Pharmaceuticals, Consultant

W221. Safety and Pharmacokinetic Profiles of MGS0274 Besylate (TS-134), a Novel Metabotropic Glutamate 2/3 Receptor Agonist Prodrug, in Healthy Subjects

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Background: Accumulating evidence suggests that hypofunction of N-methyl-D-aspartate (NMDA) receptor plays an important role in the pathophysiology of schizophrenia. Hypofunction of NMDA receptors located on GABAergic interneurons results in a disinhibition of pyramidal neurons and leads to an increase in glutamate release in the prefrontal cortex. Since activation of metabotropic glutamate 2/3 (mGlu2/3) receptors presynaptically reduces glutamate release, an mGlu2/3 receptor agonist could be a novel therapeutic target for schizophrenia.

MGS0008 is a potent and selective agonist of mGlu2/3 receptors. Pre-clinical studies indicate that MGS0008 reduces excitatory neurotransmission through activation of pre-synaptic mGlu2/3 receptors and that MGS0008 may have a therapeutic potential to treat positive symptoms and cognitive dysfunction in schizophrenia through normalization of brain activity without extrapyramidal side effects. MGS0274 besylate, the active ingredient of TS-134, is a prodrug of MGS0008. TS-134 is being developed for the treatment of schizophrenia.

Methods: Phase 1 single-ascending dose (SAD) and multiple-ascending dose titration (MAD/Titration) studies were conducted in healthy adult male and female subjects. Both studies were randomized, double-blind, and placebo-controlled.

In the SAD study, which included 4 cohorts, the safety, tolerability and pharmacokinetics (PK) of single oral doses of TS-134 were studied under fasted or fed condition at doses up to 20 mg. In one cohort, following single-blind administration of 10 mg TS-134 under fed condition, concentrations of MGS0008 in the cerebrospinal fluid (CSF) were measured for up to 24 h post-dose. Each cohort included at least 8 subjects who were randomized to receive TS-134 (6) or placebo (2), with the exception of the CSF cohort in which all subjects were treated with TS-134.

In the MAD/Titration study, the safety, tolerability and PK of multiple daily oral doses of TS-134 were studied under fed conditions at doses up to 80 mg for 14 days with 6 cohorts. Each cohort included at least 10 subjects who were randomized to receive TS-134 (8), or placebo (2).

Results: In the SAD study, a total of 33 healthy volunteers (HVs) were enrolled, of which 27 received 5-20 mg of TS-134 and 6 received placebo. In the MAD/Titration study, a total of 59 HVs were enrolled, of which 47 received 5-80 mg of TS-134 and 12 received placebo.

Following administrations of TS-134, MGS0274 reached peak plasma concentration (Cmax) within 1 h, then declined with a mean half-life (t1/2) of 0.8765 to 1.669 h for single dose and 1.055 to 10.52 h for multiple doses. Following single dose and multiple dose/titration administrations, MGS0274 was rapidly converted into its active metabolite MGS0008, which reached its Cmax 2 to 4.5 h post-dose. The t1/2 of MGS0008 was 6.909 to 8.699 h for single dose and 8.092 to 10.91 h for multiple doses. In the MAD study, mean MGS0008 Cmax and area under the concentration-time curve (AUC) increased dose-proportionally and the mean plasma trough concentrations appeared to reach steady state by 2 days after initiating fixed multiple doses. After single and multiple dose administrations of TS134, the molar ratio of MGS0008 AUCs were approximately twenty-fold higher than those of MGS0274.

In the CSF, MGS0008 concentrations peaked at 8.0 h following single dose administration of TS-134 (10 mg) and were measurable for up to 24 h post-dose. The CSF to plasma ratios of Cmax, AUC0-24h and AUC0-last were 3.67%, 4.94% and 4.94%, respectively. At this low dose, the observed CSF exposure of MGS0008 in HVs reached approximately one-sixth the exposure level (AUC0-24h) in rats, at which antipsychotic action was observed.

There were no deaths or serious adverse events in either study. Following single dose administration, the most frequent treatment-emergent adverse events (TEAEs) overall included vomiting (8 of 27 [29.6%]) and nausea (6 of 27 [22.2%]). The

incidence of vomiting and nausea appeared to increase in a dose-related manner and was considered to be dose limiting. Following a single dose of 20 mg under fasted conditions, vomiting occurred in 4 of 7 (57.1%) subjects (of which 2 were severe) and nausea in 3 of 7 (42.9%) subjects (of which 1 was severe).

In the MAD/Titration study, there were no severe TEAEs and no TEAE leading to subject withdrawal during the study. Thirty-six (36) of 47 subjects (76.6%) treated with TS-134 reported 125 TEAEs and 3 of 12 subjects (25.0%) treated with placebo reported 9 TEAEs. The most frequently reported TEAEs were headache (34.0%), nausea (31.9%), somnolence (19.1%) and dizziness (17.0%). There was no apparent dose related increase in incidences of any of the TEAEs.

No clinically-relevant trends were noted in vital signs or ECG, and individual abnormal laboratory findings were clinically unremarkable in both studies.

Conclusions: TS-134 (active ingredient: MGS0274 besylate) is orally bioavailable in humans, converts rapidly and extensively to MGS0008 and exhibits a good brain penetration profile.

Orally administered TS-134 in HVs was generally safe and well-tolerated up to 10 mg as a single dose, and up to 80 mg when administered daily using the multiple dose titration schemes for 14 days.

TS-134 is a promising candidate for further clinical development for the treatment of schizophrenia.

Keywords: Metabotropic Glutamate Receptor 2 (mGluR2), Metabotropic Glutamate Receptor 3 (mGluR3), Schizophrenia, Pharmacokinetics, Safety

Disclosure: Taisho Pharmaceutical R&D Inc., Employee

W222. Nicotinic and NMDA Receptors: Nuts and Bolts of Schizophrenia

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Background: Cognitive impairments are core features of schizophrenia and the best predictor of functional outcome. Cholinergic system and alpha-7 nicotinic acetylcholine (α-7nACh) receptors are strongly implicated in the pathophysiologic mechanisms associated with cognitive impairments in schizophrenia. Galantamine is not only a reversible, competitive inhibitor of acetylcholinesterase but also an allosteric modulator of α-7nACh receptors. The objective of this meta-analysis was to examine the efficacy of galantamine for positive, cognitive, and negative symptoms of schizophrenia.

Methods: Seven randomized controlled trials (RCTs) with galantamine in schizophrenia have been conducted to date. Both men and women were included in these studies. The primary outcome for this meta-analysis was cognitive performance, as measured by the neuropsychological tests or tasks administered in each study. The Jadad scale was used by two independent reviewers to assess the quality of the seven studies as either high or low based on a Jadad score ≥ 3 or < 3, respectively.

Results: In the meta-analysis that included six RCTs (N = 226; one study that used galantamine 32 mg [antagonistic action] was excluded), cognitive impairments were significantly improved with galantamine compared to placebo, with an effect size of 0.233. In the meta- analysis of five RCTs that used galantamine 24 mg (the two studies that used galantamine 16 mg and 32 mg, respectively, were excluded), the effect size for cognitive enhancement was 0.269. Although not statistically significant, positive and negative symptoms also improved in the galantamine group compared to placebo.

Conclusions: On the basis of the results from all the failed studies to date in schizophrenia, targeting only one pathophysiologic mechanism may be insufficient to detect a clinically meaningful signal. Nicotinic-cholinergic and glutamatergic/N-methyl-D-aspartate (NMDA) systems have not been concurrently targeted in schizophrenia in an RCT. In an open-label study, a galantamine and memantine (medication acting on the glutamatergic/NMDA system) combination improved several cognitive domains in participants with schizophrenia. In a meta-analysis of RCTs with memantine in schizophrenia, cognitive and negative symptoms were significantly improved compared to placebo. The efficacy signal was detected with galantamine and memantine despite the RCTs having several limitations and methodological issues. The synergistic action of the galantamine-memantine combination is well documented. Hence, an RCT with this combination is warranted.

Keywords: Schizophrenia, Galantamine, Meta-analysis

Disclosure: Nothing to disclose.

W223. Psychotomimetic but Not Antidepressant-Like Effects of NMDA-R Antagonists Involve the Blockade of GluN2C Subunits, Predominantly Expressed in the Cerebellum

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Background: Sub-anesthetic doses of ketamine evoke rapid and persistent antidepressant effects in treatment-resistant depressed patients through still poorly-known mechanisms. Ketamine also evokes transient psychotomimetic effects, shared by other non-competitive NMDA-R antagonists such as phencyclidine (PCP) and dizocilpine (MK-801), which are used as pharmacological models of schizophrenia. Previous studies indicate that PCP activates thalamo-cortical circuits after the blockade of NMDA-R in reticular thalamic GABAergic neurons. Since the GluN2C subunit is densely expressed in thalamus and cerebellum, we hypothesized that the psychotomimetic effects induced by NMDA-R antagonists would be partly attenuated in absence of the GluN2C subunit while antidepressant-like effects induced by ketamine would be preserved.

Methods: We examined the behavioral (N = 6-10/group) and neurochemical (N = 8-9/group) effects of ketamine, MK-801, PCP and saline in male wild-type (WT) and GluN2C receptor subunit knockout (GluN2CKO) mice. Behavioral assessments included the total distance moved and the movement pattern (meandering), which were videotaped and automatically recorded, together with rearings, number of falls, hindlimb abduction and circling, which were directly scored by an experimenter blind to genotype. Sensory gating was measured by the pre-pulse inhibition test (PPI). Motor coordination was evaluated by the rotarod test. Antidepressant-like effects of ketamine were assessed by the tail suspension test. In vivo microdialysis studies were conducted to examine ketamine effects on extracellular serotonin (5-HT) and glutamate (Glu) levels in the medial prefrontal cortex (mPFC). The distribution of NMDA-R subunits in WT and GluN2CKO mice, as well as the effects of NMDA-R antagonists on brain c-fos mRNA expression, were examined by in situ hybridization (N = 4-6/group). Statistical analyses were carried out using unpaired t-test or two-way ANOVA followed by Newman-Keuls post hoc comparisons. In all cases the level of significance was set at p < 0,05.

Results: All three NMDA-R antagonists induced psychotomimetic effects in both genotypes. While locomotor activity was increased in GluN2CKO mice ($p < 0,05$ for all three drugs), stereotyped behaviors like circling and ataxia signs (falls, hindlimb abduction) were dramatically attenuated (circling: $p < 0,01$ and $p < 0,05$ for PCP and MK-801, respectively; ataxia signs: $p < 0,05$ for all three drugs), suggesting a better motor coordination in absence of the GluN2C subunit. In agreement, GluN2CKO mice spent more time on the rotarod compared to WT mice after PCP or MK-801 administration ($p < 0,05$ and $p < 0,01$ for PCP and MK-801, respectively). However, there were no genotype differences in the PPI test. Moreover, NMDA-R antagonists evoked a general pattern of c-fos activation, except in cerebellum, where significant reductions and genotype differences were noted. Regarding NMDA-R subunits distribution, deletion of GluN2C produced remarkable changes in the expression of GluN1 subunits in cerebellar areas Crus1, simple lobule and lobule 4/5 from the cerebellar vermis ($p < 0,05$ for all areas). On the other hand, minor changes in the expression of GluN2A, GluN2B, and GluN2D subunits were found. Finally, antidepressant-like effects induced by ketamine in the tail suspension test (reduced immobility) were comparable in both genotypes. Nevertheless, after ketamine administration, GluN2CKO mice showed a significantly lower increase of extracellular 5-HT levels in the mPFC compared to WT mice ($p < 0,01$), although the glutamate increase was similar in both genotypes.

Conclusions: The GluN2C subunit appears to be strongly involved in motor components of the psychotomimetic syndrome induced by non-competitive NMDA-R antagonists, but not in the antidepressant-like effects induced by ketamine. Its genetic deletion results in an improved motor coordination after NMDA-R blockade. This supports the presence of GluN2C-containing NMDA-R in cerebellar circuits controlling motor activity and equilibrium, which are sensitive to the action of ketamine, PCP, and MK-801. This view is also supported by genotype differences in c-fos expression in cortical cerebellar areas following drug exposure. Overall, the present study supports the involvement of cerebellar GluN2C subunits as a key element in the psychotomimetic actions of non-competitive NMDA-R antagonists and suggests that GluN2C antagonists might be used to reduce the psychotomimetic effects of ketamine when used as an antidepressant.

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Keywords: GluN2C Subunit, NMDA-R Antagonists, Cerebellum, Psychotomimetic Effects, Ketamine

Disclosure: Nothing to disclose.

W224. Samidorphan, an Opioid Receptor Antagonist, Mitigates Olanzapine-Induced Metabolic Dysfunction in Female Rats

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Background: Olanzapine (OLZ) is considered to be one of the most efficacious first-line atypical antipsychotic agents (Leucht et al, 2013; Lieberman et al, 2005), but its use is limited by frequent observations of weight gain and metabolic dysfunction (De Hert et al, 2011; Lieberman et al, 2005). ALKS 3831, a flexible dose of olanzapine and a fixed dose of samidorphan (SAM), is currently under development for the treatment of schizophrenia. SAM binds with high affinity to human μ-, κ-, and δ-opioid receptors and acts as a μ-opioid receptor antagonist, with low intrinsic activity at κ- and δ-opioid receptors (Bidlack et al, 2018). The addition of SAM is designed to mitigate the metabolic side effects associated with OLZ administration while maintaining its clinical efficacy. In previous studies in male and female rats using clinically relevant plasma concentrations of OLZ and SAM, co-administration of SAM normalized OLZ-induced increases in adiposity in both sexes and attenuated OLZ-induced weight gain in females. Similarly, in female monkeys, co-administration of SAM attenuated OLZ-induced weight gain and adiposity when administered at clinically relevant concentrations. To further understand the metabolic drivers of increased weight gain and adiposity, the current nonclinical studies were designed to assess the effects of OLZ and SAM on glucose clearance and insulin sensitivity in female rats prior to measurable changes in weight and/or body composition.

Methods: Femoral artery catheterized female Sprague Dawley rats (12 weeks; ~250-275 g; 8-12 rats per group) were used for all studies. Rats were housed, managed and cared for in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011) and experiments were approved by the Alkermes Institutional Animal Care and Use Committee. All Rats were treated with a long acting injectable formulation of OLZ pamoate (100 mg/kg; SC) in combination with SAM administered via osmotic mini pump (~40 ug/hr) for 48 h prior to testing. An insulin tolerance test (ITT) to assess whole body glucose clearance following bolus insulin administration (0.375 U/kg) was performed following OLZ and SAM. A hyperinsulinemic euglycemic clamp (HIEC) was used to assess insulin sensitivity, glucose turnover, glycolysis and glycogen synthesis in a separate group of rats following OLZ and SAM administration. At study termination, adipose (inguinal and retroperitoneal), muscle (extensor digitorum longus and gastrocnemius) and liver tissues were harvested to measure glucose uptake. To assess glucose clearance following bolus insulin injection, the average change from baseline was analyzed using a mixed model repeated measurements with an unstructured variance-covariance matrix. HIEC experiments were analyzed with a two-way analysis of variance (ANOVA) followed by post hoc analysis (Tukey HSD). To assess changes in glucose uptake, treatment effects were analyzed using a one-way ANOVA followed by post hoc analysis (Fisher's LSD).

Results: In the ITT studies, olanzapine significantly ($p < 0.05$) decreased glucose clearance following bolus insulin administration. SAM had no effect alone but restored whole body glucose clearance in OLZ-treated rats. In HIEC experiments, OLZ and SAM alone and in combination did not affect glucose turnover, glycolysis or glycogen synthesis. OLZ alone however decreased both hepatic insulin sensitivity ($p < 0.001$) and glucose uptake in muscle ($p < 0.001$) while increasing uptake in adipose tissue ($p < 0.05$). Co-administration of SAM did not restore hepatic insulin sensitivity but did restore and partially restore glucose uptake in fat and muscle tissues, respectively.

Conclusions: The current studies indicate that OLZ decreases the rate of glucose clearance and/or whole-body insulin sensitivity. Based on the HIEC study, this effect can largely be attributed to an OLZ-induced decrease in hepatic insulin sensitivity. The ability of SAM to mitigate these effects was mixed as it did not affect OLZ-induced changes in glucose infusion rates within the rodent clamp study but did normalize OLZ-induced changes in glucose clearance in rodents after bolus insulin administration. OLZ-induced weight gain and adiposity may be driven by decreased glucose availability in muscle and increased glucose availability in adipose tissue, leading to an abnormal accumulation of glucose storage in adipose tissue. The major benefit of SAM appears to be blockade of adipose glucose uptake and subsequent prevention of changes in body composition produced by OLZ. Based on these data, SAM mitigates several metabolic abnormalities associated with OLZ in the absence of weight gain.

Keywords: Olanzapine, Opioid Antagonist Treatment, Schizophrenia, Antipsychotics

Disclosure: Alkermes, Inc., Employee

W225. Modulation of Peripheral Down-Stream Kynurenine Metabolism Attenuates Olanzapine-Induced Metabolic Syndrome in Mice

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Background: Dysregulation of kynurenine pathway (KP) of tryptophan (Trp) metabolism was suggested as one of the mechanisms of development of metabolic syndrome (Mets) [Oxenkrug (2010) Metabolic syndrome and dysregulation of tryptophan-kynurenine metabolism. Ann. N.Y. Acad. Sci.,1199:1-14]. KP dysregulation and MetS are highly prevalent in schizophrenia (SZ) patients, especially treated with antipsychotic medication. Kynurenine (Kyn) metabolism is trifurcated into formation of 3-hydroxykynurenine (3HK) (major route), and anthranilic (ANA), and kynurenic (KYNA) acids. We reported a shift of Kyn metabolism from formation of 3HK toward production of ANA, KYNA and 3HK metabolite, xanthurenic acid (XA), in plasma of Zucker fatty rats (MetS model), and patients with type 2 diabetes and SZ. We suggest that high prevalence of MetS in schizophrenia is mediated by dysregulation of peripheral down-stream Kyn metabolism. Therefore, correction of KP dysregulation might prevent/treat MetS in SP.

Methods: Olanzapine (4 mg/kg, p.o., 5 days/week) and/or benserazide (100 mg/day, p.o.) were administered to 6 weeks old C57Bl male mice 5 days/week for 12 weeks. Difference ($p < 0.05$) were considered as statistically significant (Mann-Whitney two-tailed test). Study was approved by the Tufts Institutional Animal Care and Use Committee and conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Results: Benserazide attenuated excessive weight gain [by 30%], impairment of glucose tolerance, and triglycerides elevation [by 25%] induced by olanzapine.

Conclusions: Present results suggest peripheral down-stream Kyn metabolism as a new target for prevention/treatment of MetS-induced by antipsychotic medications Kyn, ANA and KYNA might promote obesity via activation of aryl hydrocarbon receptors, while XA impairs pro-insulin biosynthesis and insulin activity. Benserazide has a good translational potential as medication already approved for human use.

Keywords: Kynurenine, Metabolic Syndrome, Anti-Psychotics, Benserazide

Disclosure: Nothing to disclose.

W226. Simultaneous Assessment of Surface Electroencephalogram (EEG) Activity During a Fear-Based Cognitive Behavioral Platform in Mice

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Background: One challenge of pre-clinical research of psychiatric disorders is identifying biomarkers in rodent models that are robust and potentially translatable for human clinical trials. The use of electroencephalogram (EEG) is a promising method for biomarker development, as it is relatively low-cost and surface recording EEG features are largely consistent across species. There are many established methods for passive EEG recording and analysis, such as event-related potentials and examination of sleep stages. However, there has been significantly less work exploring the use of EEG recorded in mice actively engaging in cognitive tasks. The development of this type of platform could serve both as a tool for investigating dysfunctional circuitry of transgenic mouse disease models as well as for biomarker development for clinical trials.

Methods: As fear conditioning is translatable and produces a robust and well-characterized physiological biomarker, we developed a cued fear-based EEG platform. The 2 EEG/1 EMG system from Pinnacle Technologies was used to record mouse surface EEG prior to and 24 h following fear conditioning. We analyzed post-conditioning EEG during the replay of the tone paired with foot shock (CS +) as well as during the behavioral read-out of freezing. First, we developed our paradigm by assessing EEG biomarkers in WT mice. We next validated if this paradigm was capable of detecting impaired cognition measured by behavior/EEG changes by testing an animal model with cognitive impairment. For this, we used our fear paradigm with calcium/calmodulin-dependent protein kinase II heterozygous knockout (CAMKIIa-hKO) mice that present a wide array of impairments in cognitive tasks.

Results: As expected, wild-type mice re-exposed to CS + 24 h following fear conditioning exhibit an increase in 4-6 Hz theta oscillatory EEG activity compared to their own pre-conditioning baseline. Interestingly, we find that at rest CAMKIIa-hKO mice display significantly lower power in the 4-6 Hz range than the control group. During fear recall, CAMKIIa-hKO mice exhibited both a behavioral impairment in freezing as well as significantly less 4-6 Hz power as compared to wild type littermates.

Conclusions: These findings demonstrate that surface EEG recordings during fear recall is a potentially viable method of producing electrophysiological biomarkers of cognitive behavior. In a novel set of results, CAMKIIa-hKO mice exhibited changes in surface EEG recordings both at baseline as well as during behavior that appear correlated to their cognitive deficits. This testing paradigm may be readily translatable to clinical trials for cognitive treatment indications, as similar changes in EEG has been observed during cognitive behavior in humans as well. This could have broad impact on the efficacy of pre-clinical testing of new drugs for cognitive symptoms, as cognitive dysfunction is a trait shared by a number of psychiatric and neurological disorders with few treatment options.

Keywords: EEG, Behavior, Mouse Model, Fear Conditioning

Disclosure: Astellas Research Institute of America LLC, Employee

W227. Abnormalities in the TMS-Evoked Frontal Oscillatory Activity of First-Episode Psychosis Patients

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Background: The combination of transcranial magnetic stimulation (TMS) with high-density EEG (hd-EEG) allows probing the oscillatory properties of cortical neurons, including in frontal areas, directly and non-invasively. As such, TMS/hd-EEG has been increasingly utilized to characterize frontal oscillatory dysfunctions in chronic patients with schizophrenia. The present study

investigated, for the first time, the evoked EEG responses of first-episode psychosis (FEP) patients and healthy controls (HC) after TMS of a frontal area, the motor cortex

Methods: TMS at 110% of resting motor threshold was performed in thirteen FEP patients and eleven HC while recording hd-EEG. TMS-evoked EEG potentials were analyzed both in the time and frequency domains

Results: In the time domain, TMS-evoked EEG responses of FEP were reduced in amplitude compared to HC, though this reduction failed to reach significance. In the frequency domain, FEP patients had significantly reduced activity in the beta/low gamma bands (20-37 Hz), whereas they had significantly greater activity in the alpha (8-14 Hz) band compared to HC. Furthermore, in FEP patients a higher activity in the alpha band was associated with worse positive symptoms, while a greater beta/low gamma activity was predictive of fewer psychotic symptoms.

Conclusions: By showing the feasibility of TMS/hd-EEG in acute, early course psychosis, and by demonstrating abnormal TMS-evoked EEG oscillations in these patients, this study demonstrates that TMS-related measures can identify brain abnormalities at illness onset, which in turn could lead to more effective, early treatment interventions for schizophrenia and related psychotic disorders.

Keywords: TMS-EEG, Neural Oscillations, First Episode Psychosis

Disclosure: Nothing to disclose.

W228. Activity of Neuronal Subpopulations in the Mouse Dentate Gyrus Correlates With Specific Social and Exploratory Behaviors

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Background: Human neuroimaging studies demonstrate structural and functional abnormalities of the hippocampus (hip) in multiple neuropsychiatric conditions, including schizophrenia spectrum disorders and post-traumatic stress disorder. These conditions are associated with significant disruption of social behaviors resulting in functional impairment. However, compared to its role in learning and memory, relatively little is known about the role of the hip and dentate gyrus (DG) in the regulation of specific social behaviors. We investigated this question using fiber photometry (FP) in awake mice performing exploratory and interactive behaviors.

Methods: To evaluate the magnitude and timing of bulk neuronal activity in the DG during social and non-social behaviors, the calcium indicator GCaMP6s (6s) was expressed by infusion of adeno-associated virus (AAV) into the DG of adult male mice followed by implantation of a 3 mm fiber optic cannula. The following virus and mouse pairs were studied: AAV1-Syn-GCaMP6s + C57BL/6 J wild type (constitutive expression of 6 s in all neuronal subtypes); AAV-DJ-CaMKIIα-GCaMP6s + C57BL/6 J wild type (granule cell-selective expression of 6 s); and AAV1-Syn-Flex-GCaMP6s + GAD65-Cre C57BL/6 (GABAergic interneuron-selective expression of 6s). Mice were single housed for at least 3 weeks, then FP and video recordings were conducted in home cages. After habituation, mice were recorded freely ambulating the cage for 5 mins, followed by a 10 min interaction with a male conspecific. This session was repeated for two additional days with the same conspecific to assess the effect of increasing familiarity. Signal processing and quantification was performed with MATLAB, cage location was quantified using Noldus Ethovision XT, and behavior was manually annotated at 1 Hz. Behavioral subtypes quantified were: approach, interaction, withdrawal, ambulation, rearing, resting, and resting + head movements. Because aggressive interactions were also of interest, only male mice were studied in these experiments.

Results: Dynamic 6 s calcium signal was observed in constitutively-expressed 6 s as well as in GAD65 + and CaMKIIα + neurons. Analysis of the calcium signal from constitutively-expressed 6 s in the DG ($N = 8$) demonstrated a small but significant correlation with velocity, and therefore velocity was controlled for in exploration analyses. As an initial, straightforward method to examine intrinsic safety signals, calcium signal was compared between when the mouse was localized in the corner in which it spent the majority of time (i.e. "preferred corner") or in the remainder of its cage. Calcium signal magnitude was significantly determined by cage location for all velocity ranges (location x velocity range: $p < 0.001$), and the magnitude of the signal difference in the preferred versus non-preferred regions correlated with time spent performing exploratory behavior ($p < 0.05$). During social interactions with a conspecific, mean calcium signal differed significantly by behavioral subtype ($p < 0.05$), with greatest mean signal observed during approach and withdrawal behaviors. Preliminary experiments in GAD65-Cre mice similarly demonstrated differential activity patterns during exploration behaviors. Further analysis of 6 s activity in DG GAD65 + and CaMKIIα + neurons is ongoing. Finally, we previously found that GTS-21, an alpha-7 nicotinic receptor partial agonist, reduced aggressive behavior in mice. Alpha-7 was previously shown to be preferentially expressed on GABAergic neurons in the DG and hip. Consistent with this localization, we found that systemic GTS-21 inhibits activity of constitutively expressed 6 s in the DG, while 6 s signal specifically from GAD65 + neurons is enhanced. These data support previous ex-vivo evidence for augmentation of DG/hip inhibition by GTS-21.

Conclusions: Our findings demonstrate that FP is a feasible method to record from the DG and hip in behaving animals. Furthermore, our preliminary data suggest that calcium dynamics in the DG both overall and in specific cellular subtypes are meaningfully reflective of specific exploratory and social behaviors. The intrinsic and extrinsic connectivity, as well as pharmacological expression profile of the hip/DG and subfields, are well established, and therefore this brain region might represent a plausible treatment target for impaired social behaviors as a consequence of neuropsychiatric disease. Future studies will 1) further quantify the relationship between specific cellular activity and social behaviors, including assessment of individual cellular activity by in vivo microscopy, and 2) use causal neuroscience techniques to understand the specific role of individual neuronal subtypes in social behaviors.

Keywords: Hippocampus, Dentate Gyrus, Social Behavior, In Vivo Calcium Imaging

Disclosure: Nothing to disclose.

W229. Sex Differences in Oral Oxycodone Self-Administration in Rats

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Background: Prescription opioid abuse has evolved into a severe public health problem, with an annual cost of approximately $53.4 billion dollars due to lost wages, health expenses, and criminal costs. Overdose deaths from prescription opioids have nearly quadrupled in the last 15 years. One of the most commonly abused of the prescription opioid drugs is oxycodone; in 2013, over 50 million prescriptions were written for oxycodone-

containing drugs. While oral intake is the most common route of administration in people who use prescription opiates, there is a lack of literature examining oral self-administration using rodent models.

Methods: Male and female rats were first trained to self-administer liquid oxycodone solution in operant chambers on a Fixed Ratio schedule. Progressive ratio sessions were used to assess motivation for drug delivery. After extinguishing lever pressing by substituting water for oxycodone solution, lever pressing was reinstated using oxycodone priming injections. Also examined was the impact of naloxone treatment on oxycodone self-administration rates.

Results: Evidence that rats actively self-administered oral oxycodone for its reinforcing properties include the following: significantly reduced lever pressing when water was substituted for oxycodone, renewal of responding when oxycodone access was restored, and a reduction in responding following treatment with the mu opioid receptor antagonist naloxone. Interestingly, female rats self-administered significantly more oxycodone than males. This effect was replicated across two different rat strains. Self-administration rates are not affected by estrous phase, although we observed disruptions to normal estrous cycling in females given access to oxycodone. Additionally, motivation for oxycodone self-administration (measured using progressive ratio schedule) and drug-primed reinstatement is increased in females relative to males.

Conclusions: Taken together, these findings suggest that rats will actively self-administer oral oxycodone solutions and that this can be used to model prescription opiate abuse. In this model, females show significantly increased oxycodone seeking behaviors relative to male rats.

Keywords: Prescription Opioids, Sex Differences, Self-Administration

Disclosure: Nothing to disclose.

W230. Male HIV-1 Transgenic Rats Show Lower Levels of Cocaine Self-Administration Compared to the F344/N Wildtype Background Strain

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Background: The HIV-1 transgenic (Tg) rat contains a gag-pol-deleted HIV-1 provirus regulated by the viral promotor located on chromosome 9 against the F344/N background strain (WT). There is accumulating evidence that the use of the Tg rat model is valuable to increased understanding of HIV-associated neurocognitive disorders (HAND), including substance use disorders. However, most of that research has provided experimenter-administered drugs of abuse rather than self-administration methodology in which rats can titrate their own drug intake. The very few studies that have used self-administration procedures have shown mixed results.

Methods: Adult male Tg ($n = 8$) and WT ($n = 10$) rats were fitted with intravenous catheters and given seven daily 1-hr self-administration sessions at 0.1 mg/kg/infusion cocaine on a fixed ratio (FR)1 schedule with a 20-sec time out period. Evidence of robust acquisition of cocaine self-administration did not emerge (see Results). We therefore attempted several approaches designed to boost self-administration in these rats. Session 8 was an auto-shaping session that promotes an association between drug and active lever. On this session, the active lever was inserted into the chamber for a maximum of 15 seconds. After 15 seconds, the lever was retracted, and an 'unearned' drug infusion was delivered. If the lever was pressed within the 15 seconds, the lever was retracted and an 'earned' infusion was delivered. The appropriate lever was inserted 15 times in a session on a variable interval (VI)120 sec schedule. All rats then returned to self-administration. Sessions 9 and 10 were again FR1 with 0.1 mg/kg/inf cocaine. For sessions 11-17, we increased the dose to 0.3 mg/kg/inf. Sessions 18-20 were returned to 0.1 mg/kg/inf, and sessions 21-27 were at 0.08 mg/kg/inf. We then shifted the schedule of reinforcement to a variable ratio (VR)3 in order to better assess motivation for the drug. Rats remained on this schedule for 0.08 mg/kg/inf cocaine for sessions 28-35. Rats were returned to FR1 for sessions 36-42, and then shifted dose to 0.04 mg/kg/infusion for sessions 43-50.

Results: F344 wildtype rats more readily acquired cocaine self-administration than their HIV-1 transgenic counterparts. At the initial FR1 stage, active lever pressing was greater in WT rats than in Tg rats on sessions 15-27 [Session: $F(25,400) = 7.027$, $p < .001$, $\eta p2 = .305$; Genotype: $F(1,16) = 13.050$, $p = .002$, $\eta p2 = .449$; Session x Genotype: $F(25,400) = 6.692$, $p < .001$, $\eta p2 = .295$]. During the VR3 stage, WT rats maintained significantly higher active lever pressing than Tg rats across sessions 28-35 [Session: $F(7,112) = 1.825$, $p = .089$, $\eta p2 = .102$; Genotype: $F(1,16) = 10.418$, $p = .005$, $\eta p2 = .394$; Session x Genotype: $F(7,112) = 1.781$, $p = .098$, $\eta p2 = .100$]. Throughout the final FR1 phase, WT rats maintained higher active lever pressing than Tg rats regardless of session [Session: $F(14,224) = 1.291$, $p = .214$, $\eta p2 = .075$; Genotype: $F(1,16) = 22.848$, $p < .001$, $\eta p2 = .588$; Session x Genotype: $F(14,224) = 1.447$, $p = .133$, $\eta p2 = .083$]. Using the measure of infusions, at the initial FR1 stage, WT rats ingested more cocaine than Tg rats from sessions 13 to 27 [Session: $F(25,400) = 7.436$, $p < .001$, $\eta p2 = .317$; Genotype: $F(1,16) = 13.228$, $p = .002$, $\eta p2 = .453$; Session x Genotype: $F(25,400) = 7.059$, $p < .001$, $\eta p2 = .306$]. During the VR3 stage, Tg rats consumed significantly less cocaine than their WT controls [Session: $F(7,112) = 1.784$, $p = .097$, $\eta p2 = .100$; Genotype: $F(1,16) = 10.468$, $p = .005$, $\eta p2 = .395$; Session x Genotype: $F(7,112) = 1.711$, $p = .113$, $\eta p2 = .097$]. This pattern maintained throughout the final FR1 phase [Session: $F(14,224) = 1.402$, $p = .153$, $\eta p2 = .081$; Genotype: $F(1,16) = 24.114$, $p < .001$, $\eta p2 = .601$; Session x Genotype: $F(14,224) = 1.473$, $p = .123$, $\eta p2 = .084$]. For Tg rats only, active lever pressing did not differ from inactive lever pressing until the final FR1 stage. There were no effects in the first FR1 phase, sessions 1-27 [Session: $F(25,175) = 1.361$, $p = .129$, $\eta p2 = .163$; Lever: $F(1,7) < 1$; Session x Lever: $F(25,175) < 1$], or effects in the VR3 stage, sessions 28-35 [Session: $F(7,49) = 1.287$, $p = .277$, $\eta p2 = .155$; Lever: $F(1,7) = 1.755$, $p = .227$, $\eta p2 = .200$; Session x Lever: $F(7,49) < 1$]. However, greater active than inactive lever pressing emerged in the final FR1 stage, sessions 36-50 [Session: $F(14,98) = 1.599$, $p = .093$, $\eta p2 = .186$; Lever: $F(1,7) = 6.030$, $p = .044$, $\eta p2 = .463$; Session x Lever: $F(14,98) = 1.380$, $p = .178$, $\eta p2 = .165$].

Conclusions: There are dramatic differences in cocaine self-administration by Tg compared to WT, even after implementing some behavioral 'tricks' to increase consumption. Despite these efforts, fewer than half of the Tg rats showed reliable self-administration by the end of the 50-session training regimen. In contrast, 8 of the 10 WT rats showed active lever discrimination soon after the autoshaping session (Session 8); high, consistent rates of active lever pressing emerged for the remaining two WT rats at the end of the VR3 stage (Session 35). These results may contribute supporting evidence for the differential sensitivity to cocaine between Tg and WT rats, and they certainly highlight the need to carefully evaluate and consider the behavioral components of studies using this transgenic model. The full disclosure of the pattern of self-administration acquisition that we observed should aid other researchers interested in investigating comorbidities between HAND and substance use disorders in self-administering rats.

Keywords: HIV-Associated Neurocognitive Disorder, Cocaine Self-Administration, Behavioral Analysis, Neuroimmunology, Motivation

Disclosure: Nothing to disclose.

W231. Lasting Effects of Increasing Nucleus Accumbens Activity on Binge-Like Alcohol Drinking and the Transcriptome in Mice

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Background: The prevalence of alcohol abuse is > 26% in the US population. The socioeconomic burden associated with alcohol is an $249 billion/year, where 75% of this cost is related to binge drinking. Binge drinking is defined by the NIAAA as having 4-5 drinks within 2 h and/or achieving a blood alcohol level (BAL) > 80 mg%. Binge drinking is a problematic pattern of behavior and often leads to alcohol use disorders (AUD). While the adverse consequences of binge drinking are clear, mechanisms that underlie this dangerous pattern of behavior are not well understood. Further, there is a public health need for more effective treatments to reduce harmful drinking. To model binge drinking we use a schedule called "Drinking in the Dark" (DID), where mice receive 2 h access to a 20% ethanol solution early in their active cycle (3 h after lights off). This procedure induces robust levels of alcohol drinking accompanied by intoxication (BAL > 80 mg%). We previously found that we could use Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to bidirectionally modulate binge drinking in mice. Here, we test whether chronically manipulating NAc activity can produce lasting effects on drinking in a line of selectively bred High Drinking in the Dark (HDID) mice.

Methods: To determine whether chronic manipulation of NAc activity would produce lasting effects on binge drinking, we stereotaxically injected HDID mice with AAV2 hSyn-HA hM3Dq, -hM4Di, or -eGFP bilaterally into NAc (n = 12,6,13 respectively), and allowed 3 wks recovery before testing. Mice were initially treated with vehicle (1% DMSO in saline) 30 min prior to DID for 7d to determine baseline drinking levels. Mice were then treated clozapine-n-oxide (CNO; 1 mg/kg, IP) 30 min prior to DID for 28d to determine the effects of chronic NAc DREADD activation (excitatory or inhibitory) on drinking. Lastly, mice were again treated with vehicle prior to DID for 7d ("washout") to determine whether chronic manipulation of NAc DREADDs had lasting effects on drinking. Since increasing NAc activity produced lasting reduction in binge drinking, a second experiment was carried out in another cohort (where all mice received AAV hM3Dq infusions in the NAc). There were 2 treatment groups (mice receiving vehicle baseline/CNO/vehicle washout treatments as above, or mice receiving only vehicle) and 2 fluid groups (alcohol or water drinking mice), where n = 11-12/treatment group/fluid type. At the end of this experiment, we collected NAc tissue and processed it for RNA-Seq to identify gene expression altered by alcohol drinking and "rescued" by CNO treatment. We identified several genes of interest (e.g. HDAC4), validated them using qPCR, and used pharmacological approaches to determine whether manipulation of these targets could alter drinking. To set up the condition of chronic drinking, mice were offered access to alcohol in a DID for 2 wks, and then treated with an HDAC4/5 inhibitor (0, 5, or 20 mg/kg LMK235, IP) administered 1 h prior to DID for 2 wks. (n = 8/sex/dose). Statistics: Repeated measures ANOVAs were carried out to determine the effect of treatment period on drinking (one way) or to determine the effect of sex and dose (two way), and if appropriate, Dunnett post-hoc test was carried out to compare treatment periods with baseline. RNA-Seq data were analyzed using STAR aligner, HTSeq read counting, LIMMA normalization & differential expression, Enrichr analysis, and WGCNA.

Results: We found that chronically increasing NAc activity (via CNO/hM3Dq) decreased binge-like drinking (vehicle baseline vs CNO treatment, $p < 0.01$) in HDID mice, an effect that lasted for at least 7d (vehicle baseline vs. washout, $p < 0.05$), suggesting behavioral plasticity. Chronic NAc inhibition (via CNO/hM4Di) did not alter binge-like drinking, and chronic CNO did not alter drinking in mice expressing GFP. We performed another study and used RNA-Seq to study this behavioral plasticity on a molecular level. We again observed that chronically increasing NAc activity produced lasting reduction in alcohol drinking ($p < 0.001$). Analysis revealed significant changes in expression of several plasticity-related genes (i.e. Hdac4 and Adamts4 were increased in alcohol drinking mice as compared with water drinking mice that received vehicle injections, and expression of these genes was normalized in mice receiving chronic CNO treatment). In a separate study, we used a pharmacological approach to target HDAC4, an epigenetic modifier that regulates transcription, morphology, and plasticity. We found that chronic treatment with an HDAC4/5 inhibitor dose dependently reduced binge-like drinking ($p < 0.05$).

Conclusions: Previous studies have shown that NAc deep brain stimulation reduces drinking in animal models and rates of relapse in treatment resistant individuals with AUD; however, these effects are not lasting. Consumption, impulsivity, craving, and relapse increase when stimulation is turned off. We used DREADDs, which are G-protein coupled receptors, to induce plasticity in the NAc and produce lasting changes in the brain and on drinking behavior in mice. These results show that chronically increasing NAc activity using DREADDs can ameliorate the effects of high-intensity, binge-like drinking on a behavioral and molecular level. Further, we were able to target specific molecular pathways altered by alcohol but rescued by excitatory DREADDs using pharmacology (HDAC4/5 inhibitor) to mimic the behavioral effects of DREADDs

Keywords: Chemogenetics, Alcohol Intake, Gene Expression, HDAC Inhibitors, Genetic Animal Model

Disclosure: Nothing to disclose.

W232. Nucleus Accumbens Neuronal Ensembles in Cue-Induced Reward Seeking

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Background: Unmanaged reward seeking is a shared central feature of eating and substance use disorders that expose patients to lifelong relapse vulnerability. Recent research shows that rewarding drug-related experiences induce synchronous activation of a discrete number of neurons in the nucleus accumbens (NAcc) that are causally linked to reward-related contexts. Convergent findings using different biomarkers reveal that only ~2-5% of cells encode a putative cocaine ensemble, including deltaFosB immune-labeling, Daun02-inactivation of cFos expressing neurons, and the number of NAcc MSNs exhibiting phasic activity. When animals are exposed to two rewards, in vivo measurements of neuronal firing in NAcc reveal ~20% overlap between neurons responding to self-administration of different types of reward such as cocaine, water, regular chow or sucrose, while a study using FISH reports that 50% of activated neurons in

the infralimbic prefrontal cortex respond to both ethanol and saccharin. These results suggest a finely tuned specificity of ensembles. We characterize here the neuronal ensemble that is built through drug experience and codes for drug seeking. We additionally address the question of whether or not addictive drugs usurp circuitry used by natural rewards or involve distinct circuitry mechanisms by evaluating the segregation between cocaine- and sucrose-related ensembles within the same animal.

Methods: We use targeted recombination in active populations (TRAP) strategy, specifically FosCreERT2/+/Ai14 (cFos-TRAP) transgenic mice to deposit a cFos-driven Cre recombinase-tdTomato reporter into neurons activated during cue-induced reward seeking and extinction in order to tag cells as potentially encoding these behaviors. The construct fuses Cre-recombinase to the estrogen receptor (ER) under the cFos promoter and allows nuclear Cre expression in the presence of ER agonist 4-hydroxytamoxifen (4-OHT), specifically in the cells expressing cFos. To characterize the seeking ensemble, these mice underwent the well-described rodent behavioral model of cocaine self-administration (SA) and cue-induced reinstatement of seeking. In order to determine if reward-seeking ensemble activation is sufficient to induce seeking behavior, we injected excitatory designer receptors exclusively activated by a designer drug (Gq-DREADD) in the NAcc. Specific Cre expression permitted restricted viral expression within the seeking ensemble. To define and compare different reward-specific ensembles within the same animal, we developed a dual cocaine and sucrose self-administration paradigm in mice, where each reward is associated to a different discrete cue. After undergoing extinction training in absence of cues, mice are first re-exposed to one cue in presence of 4-OHT, allowing the tagging of the reward-specific ensemble with tdTomato, and a few days later exposed to the second cue, followed by immediate Fos tagging. Using this paradigm, we were able to assess the neurons included in the cocaine or sucrose ensembles, and to quantify the overlap between the two populations within the same animal exposed to both types of reward.

Results: We tagged with tdTomato the small number of neurons in the NAcore activated during repeated cued-induced seeking to cocaine or sucrose. The tdTomato cells were specifically activated during seeking, and not during extinction behavior or after animals remained in the home cage. Moreover, we confirmed that Gq-DREADD expression is restricted to the cocaine-seeking ensemble. Finally, we validated the dual cocaine and sucrose SA paradigm, and were able to induce reward-specific seeking in animals previously exposed to cocaine and sucrose rewards. We established that the large majority of cells (60%) in the NAcc are specifically activated during seeking of distinct rewards.

Conclusions: The data obtained here sheds new light on the ensembles in the NAcc sustaining maladaptive drug-oriented seeking behaviors and how it compares to natural rewards responses.

Keywords: Cocaine Addiction, Food Addiction, Relapse, c-Fos-Expressing Ensembles, Reward Self-Administration

Disclosure: Nothing to disclose.

W233. The Impact of Oxytocin Receptor Knockdown in the PFC on Acquisition of Cocaine Taking and Reinstated Cocaine Seeking

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Background: Oxytocin treatment may be a beneficial treatment for multiple neuropsychiatric disorders, including addiction. In animal models of contingent drug self-administration, oxytocin effectively reduces reinstated drug seeking in male and female rats. Very little is known about the underlying mechanisms governing this effect, in part because oxytocin receptors (OxyR) are ubiquitous in brain and are localized on many different types of neurons within the addiction circuit. Very little is known about the endogenous oxytocin system following exposure to cocaine within circuit largely due to the lack of sophisticated molecular tools to study the oxytocin system in rats. Previously, we demonstrated regional specificity between the prelimbic (PL) area of the medial prefrontal cortex (mPFC) and the nucleus accumbens core (NAc) on oxytocin's impact on cocaine cued reinstatement. Oxytocin directly into the PL increased, whereas NAc oxytocin decreased lever responding for cocaine conditioned cues. To better understand possible brain region-specific roles for OxyR signaling in cocaine relapse behavior, we developed an adeno-associated viral vector (AAV) expressing short hairpin RNAs to selectively degrade the rat OxyR mRNA in infected cells.

Methods: Male (Sprague-Dawley) rats received bilateral infusions of the shRNA for the oxytocin receptor (shOxyR) or a control virus (shLUC) into the PL. Rats also had intravenous catheters implanted for cocaine self-administration. Following surgery recovery, rats lever pressed for cocaine on an escalating FR ratio for 13 days, then underwent at least 8 days of extinction training, and were tested for cued and cocaine-primed reinstatement of drug seeking. During the cued reinstatement test, responses on the drug-associated lever resulted in a presentation of the light + tone stimulus complex originally associated with cocaine delivery. Before testing, rats received oxytocin (1 mg/kg, ip) or saline.

Results: OxyR knockdown in the PL delayed the acquisition of lever pressing on an FR1 schedule of reinforcement, but no differences occurred between groups once the groups had acquired and there were no differences in extinction. The shOxyR decreased cued reinstatement relative to shLUC, but a cocaine primed resulted in increased lever responding in the shOxyR group. Oxytocin administration decreased lever pressing during both types of reinstatement testing.

Conclusions: This study provides critical new information about how endogenous oxytocin in the PL functions to impact drug seeking in response to different precipitators to relapse. The tool developed to knockdown regionally specific oxytocin receptors OxyRs in rat could provide important new insights that aid development of oxytocin-based therapeutics to reduce relapse in recovering addicts and other neuropsychiatric disorders.

Keywords: Oxytocin Receptor, Prefrontal Cortex, Cocaine Reinstatement and Taking

Disclosure: Nothing to disclose.

W234. Cues Play a Critical Role in Estrous-Cycle Dependent Enhancement of Cocaine Reinforcement

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Background: While preclinical work has aimed to outline the neural mechanisms of drug addiction, it has overwhelmingly focused on male subjects. There has been a push in recent years to incorporate females; however, males and females often have different behavioral strategies, making it important to not only include females, but to develop models that assess the factors that comprise female drug addiction. Although both males and females become addicted to cocaine, females transition to addiction faster, consume more cocaine, and have greater

difficulty remaining abstinent. Clinical work shows that women also exhibit increased cue-induced craving for cocaine, indicating that sex differences in cocaine addiction may not solely be due to reinforcing effects of cocaine and may include complicated interactions with drug-associated stimuli. Here we define the influence of estrous cycle on associations between cocaine and Pavlovian cues and the influence of these cues on subsequent self-administration. Further, via assaying brain-wide activity markers following cue exposure, we define the brain regions controlling these effects.

Methods: Traditional self-administration models often include light or tone cues that serve as discriminative stimuli and/or consequent stimuli, making it nearly impossible to disentangle the effects of cue learning, the cues themselves, and acute effects of drugs. However, understanding the discrete aspects of behavior that control female drug addiction will be important as we move forward with defining therapeutic interventions that will be efficacious in both sexes. To this end, we have developed a new behavioral paradigm that combines Pavlovian instrumental transfer with behavioral economic analysis to disentangle the interaction between drug-associated cues and the consummatory and appetitive responding driven by cocaine. This task can be completed within a single session, allowing for studies looking at estrous cycle stage-dependent effects in intact cycling females, something that has been difficult in the past. 24 pavlovian pairings between a cue light and cocaine (CS +) were done on a variable time 300 schedule (VT300) over 2 sessions in female rats either during estrus (high ovarian hormones), diestrus (low ovarian hormones) or in males. Rats then acquired self-administration in the absence of cues. Next, rats moved to the test session, where the threshold procedure was conducted either in the presence or absence of the CS + . The within-session threshold testing allowed for the assessment of how the presentation of the CS + altered motivation and drug consumption during discrete cycle stages. Lastly, rats were exposed to a final CS + presentation, were sacrificed and brains were collected 60 minutes later for immunohistochemistry for c-Fos across reward structures: caudate putamen, NAc core and shell, prelimbic and infralimbic prefrontal corticies, and ventral tegmental area. Vaginal cytology was conducted daily in females in order to establish estrous cycle phase.

Results: We find that conditioned cues are critical to expression of estrous-cycle control of motivation. Further, the estrous cycle stage at which the cues acquire value is central to their ability to enhance motivation. Cues paired during estrous enhance dopaminergic circuit activity to drive drug seeking for these cues, even weeks later. When a CS + was paired during estrus its presentation during self-administration decreased sensitivity to cost (reflective of an increase in motivation), regardless of which cycle stage animals were in when they were self-administering. Further, when the CS + acquired value during estrus they engendered more responding for cue presentation in the absence of drug. The CS + presentation resulted in activation (measured by c-Fos induction) across reward related brain regions but was correlated with lever pressing in the NAc core.

Conclusions: Overall, these studies show that sex differences in cocaine reinforcement are more complicated than previously thought. Both clinical and preclinical literature have highlight female subjects as a particularly vulnerable population, necessitating a complete understanding of the factors that contribute to this vulnerability. Here we outline an important role of cues in the enhancement of self-administration in females, demonstrating fundamental differences in the sex-specific regulation of reinforcement behavior. ales and females often have different behavioral strategies, making it important to not only include females in current drug addiction models, but to also develop models that assess the factors that comprise female drug addiction. To this end, we have developed a new behavioral paradigm that combines Pavlovian instrumental transfer with behavioral economic analysis to disentangle the interaction between drug-associated cues and the consummatory and appetitive responding driven by cocaine. The strength of this task is its short timeline, allowing for studies looking at estrous cycle stage-dependent effects in intact cycling females, something that has been difficult in the past. Together, this work provides a precise behavioral mechanism for the enhancement of motivation for cocaine in females and highlights the need for more complete behavioral studies dissociating discrete aspects of motivated behaviors between the sexes.

Keywords: Sex Differences, Cocaine, Vulnerability, Self-Administration, Dopamine

Disclosure: Nothing to disclose.

W235. Correlating Cocaine-Induced Structural Changes With Altered Cognitive Performance in Rhesus Monkeys

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Background: Altered cognitive performance and structural changes in brains of patients suffering from cocaine dependence have been reported in multiple clinical studies. Due to the cross-sectional nature of these studies, it remains unclear whether these differences are caused by chronic stimulant use or whether they preceded use and may reflect a predisposition to development of drug dependence instead. Longitudinal preclinical studies can provide insight into the nature of these changes.

Methods: In this study, we obtained structural MRI scans from 14 adult male rhesus macaques and established baseline performance on a visual working memory task (Delayed Match to Sample; DMS) and a stimulus reversal learning task (RevL). Subsequently, 8 subjects self-administered cocaine intravenously, 4 days a week (up to 3.0 mg/kg/day) while control subjects performed similar tasks for water reward. Impairment of cognitive performance tested on drug free days for these subjects was published previously. After 12 months of cocaine self-administration a second set of MRI scans were obtained. We used voxel-based morphometry (VBM) to examine the treatment group by time structural interaction on gray matter density (GMD).

Results: We observed clusters of decreased GMD in the medial and lateral temporal lobe (parahippocampal fusiform gyri and along the superior temporal sulcus) in the cocaine group. In addition, clusters of decreased GMD were observed in the thalamus, superior parietal cortex, insula, and orbitofrontal and superior frontal cortex. Clusters of increased GMD in the cocaine group were observed in cerebellum, bilateral temporal poles and ventral frontal cortex, superior parietal, precentral and postcentral cortex, and rostral caudate nucleus. Most of the observed changes in GMD are consistent with the clinical gray matter alterations in stimulant-dependent patients.

Decreased GMD in 4 clusters correlated with impaired cognitive performance in cocaine-exposed subjects. The impaired performance on the DMS task showed a significant correlation with the reduced GMD in the middle temporal lobe, an area previously implicated in DMS performance. Impairments in performance on the RevL task correlated significantly with the reduced GMD in orbitofrontal cortex, a region frequently implicated in RevL performance. Finally, decreased GMD in superior frontal cortex and the superior temporal and parietal cortex correlated with impairment in both the DMS and RevL performance. Both these regions have been associated with sustained attention.

Conclusions: These present findings indicate that chronic cocaine exposure in NHP results in structural brain changes consistent with clinical observations in cross-sectional studies, suggesting they are caused by prolonged stimulant exposure rather than a pre-existing condition. Furthermore, the structural alterations are likely to functionally contribute to the cognitive impairment observed in the same subjects.

Keywords: Cocaine Addiction, Cognition, Voxel-Based Morphometry (VBM)

Disclosure: Nothing to disclose.

W236. Granulocyte-Colony Stimulating Factor (G-CSF) Potentiates Mesolimbic Dopamine Release, Alters the Synaptic Proteome of the Nucleus Accumbens, and Reduces Cue-Induced Cocaine Seeking

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Background: Pathologic use of illicit drugs represents a major public health concern and creates significant economic and social costs. Addiction to cocaine and other psychostimulants remains a major cause of this morbidity. The pathophysiological mechanisms that lead to persistent and dysregulated drug use remain incompletely understood, and there are currently no FDA-approved pharmacotherapies for treatment of psychostimulant use disorders. There is growing evidence that dysregulation of the immune system plays a role in the pathophysiology of multiple psychiatric disorders including major depressive disorder and schizophrenia. While cocaine is known to have immunomodulatory effects, the link between these immune interactions and pathological use behaviors has only recently been investigated. We recently identified granulocyte-colony stimulating factor (G-CSF) as a cytokine that is increased in serum and brain by chronic cocaine. Peripheral administration of G-CSF enhances cocaine place preference and cocaine intake in a self-administration model, and also facilitates cocaine-induced neuronal activation in the nucleus accumbens and prefrontal cortex. Here, we present additional mechanistic studies examining how G-CSF exerts its effect on the brain and demonstrate that G-CSF can alter behavioral response to cocaine in an extinction-reinstatement paradigm.

Methods: Using fast-scan cyclic voltammetry we measured dopamine release from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) in mice previously injected with saline or G-CSF (50 mcg/kg, i.p.). Effects of G-CSF on the proteomic makeup of the NAc were assessed using a 2 x 2 design of animals injected with Saline or Cocaine (7.5 mg/kg) And PBS or G-CSF once daily for seven days. Nucleus accumbens punches were then tryptically digested and protein composition assessed by tandem mass spectrometry. Quantitative analyses between groups were assessed using Scaffold mass spec analysis software. To assess the effects of G-CSF on extinction and reinstatement of cocaine seeking, Sprague-Dawley rats were first trained to self-administer cocaine on a fixed-ratio 1 schedule until stably responding. Two cohorts of animals then received daily injections of G-CSF or vehicle during extinction (Cohort 1) or incubation and reinstatement (Cohort 2). The rate of extinction and cue and cocaine-induced reinstatement were measured in both cohorts.

Results: When dopamine release in the NAc was measured, animals previously injected with G-CSF exhibited markedly increased dopamine release without any effect on uptake. Additionally, there was an interaction with cocaine, and when cocaine was put on the slice G-CSF pre-treatment further enhanced dopamine release. Proteomics analysis demonstrated a similar phenomenon pattern of effect. G-CSF treatment alone lead to statistically significant changes in 214 proteins, while treatment with G-CSF and cocaine together lead to changes in 292 proteins compared to saline controls. Pathway analyses of significantly regulated proteins demonstrate significant changes in the mammalian target of rapamycin (mTOR) and fragile x mental retardation protein (FMRP) pathways. Additionally, numerous proteins linked to synapse formation were also altered. In our behavioral assessments we find that treatment with G-CSF during extinction of cocaine seeking leads to a more rapid rate of extinction of the behavior, but no effect on reinstatement. However, treatment with G-CSF daily during abstinence and during reinstatement lead to a marked reduction in cue-induced cocaine seeking.

Conclusions: Our results demonstrate that the pleiotropic cytokine G-CSF potentiates dopamine release from the ventral tegmental area to the nucleus accumbens. Additionally, we find that prolonged treatment with G-CSF alters the synaptic proteome of the nucleus accumbens. Finally, we see that G-CSF can enhance extinction of cocaine seeking and reduce cue-induced reinstatement. These studies further the importance of G-CSF as a key signaling molecule in addiction-like behaviors and provide a solid basis for the mechanism of the effects of G-CSF in the brain.

Keywords: Neuroimmune, Cytokine, Cocaine Addiction

Disclosure: Nothing to disclose.

W237. The Role of the Rostromedial Tegmetal Nucleus in Cannabinoid Reward

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Background: Delta-9 tetrahydrocannabinol (THC) can produce unpleasant side effects including increased anxiety, but nonetheless many individuals are able to overcome these aversive consequences and persist in drug use. It is a common phenomenon for abused substances to display both rewarding and aversive properties. The rostromedial tegmental nucleus (RMTg), composed of a group of gabaergic neurons that negatively regulates midbrain dopamine transmission, has been implicated in the complex interplay between reward and aversion including as it relates to drugs of abuse. We used a combined THC and cannabidiol (CBD) intravenous self-administration model in rats to test a role for this brain region in regulating THC reward. Although not particularly robust, self-administration of THC can be achieved in rats under specific circumstances including with passive drug pre- treatment, and we have demonstrated that these modifications facilitate acquisition of behavior. Here we omitted these adjustments to assess the contribution of the RMTg to de novo acquisition of THC + CBD self-administration.

Methods: Adult male Sprague-Dawley rats were given excitotoxic ($n = 8$) or sham lesions ($n = 8$) of the rostromedial tegmental nucleus accumbens as well as implanted with intrajugular catheters. Following recovery from surgery, rats were allowed to self-administer THC:CBD in a 10:1 ratio on a fixed ratio 1 (FR1) schedule (1.5 h per day, 1-2 µg/kg per infusion) paired with discrete light and tone cues. Acquisition and maintenance of THC + CBD self-administration was compared between groups for 10 days. This was followed by 10 days of abstinence and 6 days of extinction training. Rats were tested for reinstatement (context, cue, THC prime, and yohimbine). The same animals were then cross-trained to respond for natural reward reinforcement on the previously inactive lever. Their responses were compared using an increasing FR1 through FR5 schedule followed by extinction and

cue reinstatement. All experimental protocols in animal studies were approved by the Institutional Animal Care and Use Committee at Medical University of South Carolina or the University of Minnesota and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Results: Rats with RMTg lesions showed a marked increase in active lever responding for THC + CBD compared to sham lesion animals during acquisition and maintenance of self-administration ($F(1,14) = 8.22$, $p < 0.012$). This resulted in significantly more drug infusions being delivered to RMTg lesion rats ($F(1,14) = 7.96$, $p < 0.014$). While 62.5% of the lesion rats met criteria for both number of daily infusions (> 5 infusions/day) AND lever discrimination (> 2:1 ratio) during THC + CBD self-administration, none of the sham lesion rats met both criteria. Perhaps not surprisingly, the sham rats likewise demonstrated a lack of reinstatement given the failure to acquire the behavior. In lesion rats, reinstatement levels were comparable to those observed in other well-trained animals. In contrast, the RMTg lesion did not alter responding for palatable food reward or reinstatement.

Conclusions: In summary, these data illustrate that the RMTg plays an important role in regulating THC + CBD self-administration but not operant consumption of a natural reward. Lesion of the RMTg increased lever pressing for THC + CBD and overall THC + CBD intake but surprisingly did not enhance cue-induced reinstatement behavior of the learned response. A limitation of these studies for examining the impact of the RMTg at various stages of drug use was employing a permanent lesion rather than a more acute pharmacologic or genetic manipulation. Future studies will aim to determine whether the effect of RMTg lesion is due to mediating aversive conditioning to THC.

Keywords: THC, RMTg, Self-Administration

Disclosure: Nothing to disclose.

W238. Dissociating the Signaling Mechanisms Underlying Addiction Vulnerability From the Consequences of Drug Use

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Background: Adaptive, flexible decision-making is disrupted in addicted individuals and believed, in part, to be a consequence of chronic drug use. Recent studies, however, have suggested that pre-existing alterations in decision-making might influence future drug-taking behaviors. Decision-making may be a critical biomarker for identifying the signaling mechanisms mediating addiction.

Methods: To examine this possibility, we trained rats ($N = 20$) on a novel, three-choice, probabilistic reversal-learning (PRL) task. Rats were then implanted with intra-jugular catheters and trained to self-administer methamphetamine (MA) for daily 6 h sessions over 14 days. Following 5 days of abstinence, decision-making was reassessed on the PRL. We found that decision-making processes in the PRL predicted future drug-taking behaviors in rats and were also impaired as a consequence of MA self-administration. Further, our computational analyses indicated that the reinforcing effect of positive outcomes predicted MA self-administration (Δ1 parameter), while use of negative outcomes to guide decision-making was affected by MA (Δ2 parameter). These data suggest that the processes that confer addiction vulnerability differ from the consequences of drug use. We then sought to identify specific proteins that were uniquely related to these dissociable decision-making parameters. Tissue was collected from the ventral striatum of drug naïve rats ($N = 16$) and rats with a history of methamphetamine self-administration ($N = 18$), whom had been trained on the PRL, and subjected to liquid chromatography mass spectrometry (LC-MS/MS).

Results: Of the 2900 proteins detected in drug-naïve rats, differential expression (DEX) of 294 proteins were specifically related to the Δ1 parameter, DEX of 93 were uniquely related to the Δ2 parameter, whereas DEX of only 23 proteins were related to both parameters. These data suggest that altered expression of specific sets of proteins are linked to distinct aspects of addiction pathophysiology. We then conducted a cross-correlational analysis with protein-behavior correlates in methamphetamine-exposed rats to isolate the proteins that related to the addiction vulnerability phenotype from those involved in the consequence phenotype. Using this approach, we reduced our ~300 protein candidates to three protein targets that were selectively related to the Δ1 parameter (sorting nexin 1, ryanodine receptor 2, and ataxin 2-like) and a single protein target that was related to the Δ2 parameter (Ras-related protein 3B – Rab3B).

Conclusions: Together, these data provide a innovative behavioral platform for isolating novel protein targets that could be manipulated to promote addiction resilience or treat addiction.

Keywords: Reinforcement-Based Decision-Making, Vulnerability, Addiction, Proteomics

Disclosure: Nothing to disclose.

W239. Adenosine A2A Receptor in the Dorsomedial Striatum Regulates Context-Dependent Goal-Directed and Ethanol Seeking Behaviors

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Background: The cortico-striato-pallidal circuits facilitate goal-directed behaviors in the decision-making process. Adenosine A2A receptor (A2AR)-expressing inhibitory indirect pathway in the dorsomedial striatum (DMS) contributes to the goal-directed action in the reward-seeking behavior. However, the contextual relationship of A2AR-dependent goal-directed control in ethanol-seeking behavior and the role of the inhibitory indirect circuit have not been fully investigated.

Methods: We investigated the context-dependent goal-directed behavior during ethanol-containing reward seeking session in the A2AR expressing neurons in the DMS. After training mice in the nose-poke operant chambers, we examined whether pharmacological regulation of A2AR and pre-experience of ethanol alter the goal-directed action. Then, we tested the effects of goal-directed control on the neuronal activity in the DMS. Followed by, using Y maze, we also assessed whether the mice are able to distinguish the value of ethanol depending on pre-existing goal-directed behaviors. Next, using in vivo optogenetic approaches, we further examined the role of inhibitory indirect circuit in goal-directed behavior.

Results: Pharmacological A2AR activation in the DMS dampened goal-directed behavior during the ethanol-seeking behavior in nose-poking operant chambers. Using mice exhibiting goal-directed behavior toward ethanol containing solution, our results indicate that enhanced goal-directed behavior increased A2AR-dependent ethanol value compared to non-trained group. Interestingly, pre-exposure of ethanol exacerbates the A2AR-dependent goal-directed action. Consistent with our pharmacological and behavior results, we found that enhanced goal-directed behaviors are associated with reduced neural activity in the indirect DMS neurons. Conversely, optogenetic manipulating neuronal activity in the indirect DMS circuit regulated goal-directed action in ethanol reward seeking behaviors.

Conclusions: Our study demonstrates that DMS A2AR regulates context-dependent goal-directed control. Also, we provide a novel finding that A2AR expressing cortico-striato-pallidal circuits could be a potential therapeutic target for maladaptive goal-directed control.

Keywords: Adenosine A2A Receptor, Goal-Directed Behaviors, Optogenetics, Context, Alcohol-Seeking Behavior

Disclosure: Nothing to disclose.

W240. Microglia Refine Dopamine Receptors During Adolescent Nucleus Accumbens Development: Relevance for Normal Behavior Vs. Opioid Addiction

Abstract not included.

W241. pCREB Mediates ccdc109a Gene Expression in an Epigenetic Manner in Morphine Withdrawal in Rats and Mice

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Background: Over the last decade, the opioid epidemic has become a national crisis in the USA. Individuals with opioid dependence experience a physical withdrawal syndrome when tapering off opioids. Physical dependence and the associated withdrawal syndrome is one factor that drives compulsive drug-taking behavior and short-term relapse. To date, the cellular and molecular mechanisms of morphine withdrawal (MW) remain incompletely understood. MW is characterized by persistent neuroadaptations in key brain regions, such as the midbrain periaqueductal gray (PAG). Our previous studies have shown that phosphorylated cAMP response element binding protein (pCREB), a transcription factor, is involved in the PAG in MW. However, the downstream mechanisms of pCREB in the PAG in MW is still not clear. The ccdc109a gene encodes mitochondrial calcium uniporter (MCU) protein expression. MCU mediates calcium uptake into mitochondria and plays key roles in cellular bioenergetics and activation of cell ROS pathways. In the present studies, we examined the molecular relationship of pCREB and MCU in the PAG in MW using rats and mice.

Methods: Male/female Sprague-Dawley rats or C57BL/6 mice were used. Chronic escalating doses (10-50 mg/kg) of morphine administered intraperitoneally (IP) for a period of 5 days. A withdrawal syndrome was precipitated by naloxone (4 mg/kg, IP) 1 h after the last morphine injection (day 5). Immediately after naloxone, withdrawal signs were evaluated for 30 minutes. Withdrawal score was calculated for each animal by assigning a weighting factor to the various physical signs of withdrawal (see Hao S. etc, Neuropsychopharmacology. 2011 Feb;36(3):664-76). Following MW, western blot was used to determine levels of pCREB and MCU proteins in the ventrolateral PAG. For intracranial microinjection into the PAG, cannula implantation was carried out in a stereotaxic headholder. An antisense oligodeoxynucleotide against CREB (AS-CREB), or an MCU inhibitor, was microinjected in MW rats. Chromatin immunoprecipitation (ChIP) assay was used to determine the ccdc109a gene promoter enrichment of pCREB. Over-expression of CREB was induced by microinjection of a recombinant herpes simplex virus (HSV) vector that encodes the CREB gene. Furthermore, to further verify the role of CREB in ccdc109a gene expression in MW, we used mutant mice possessing loxP sites flanking exon 2 of the CREB gene (CREB f/f). An HSV vector expressing Cre plus GFP or GFP alone was microinjected into the PAG of CREB f/f mice with MW.

Results: Chronic morphine withdrawal was precipitated by naloxone, with increased MW scores seen in rats and mice ($P < 0.05$, $n = 5$-6 rats, 7-9 mice). MW increased the expression of pCREB and MCU protein in the PAG using western blots. Immunostaining showed co-localization of pCREB and MCU in PAG neurons. Microinjection of AS-CREB, or of the MCU inhibitor, Ru360, into the PAG blunted the MW syndrome. Western blots showed that AS-CREB reduced the expression of MCU in the PAG in MW. ChIP assay showed that AS-CREB reduced the enrichment of pCREB on the MCU gene promoter region in the PAG in MW. Over-expression of CREB mediated by HSV vectors further increased MW scores and expression of MCU protein in the PAG. Injection of an HSV vector expressing Cre into the PAG of CREB f/f mice with MW reduced MW behavior scores and MCU mRNA and protein levels compared to an HSV vector expressing GFP alone.

Conclusions: Our results suggest that withdrawal from chronic systemic morphine is associated with phosphorylation of CREB and induction of MCU in PAG neurons. Further, increased enrichment of pCREB binding on the MCU gene promoter in the PAG in MW suggests that phosphorylation of CREB mediates increased expression of MCU in an epigenetic manner, which is supported by findings using CREB f/f mice. Understanding the complex relationship between pCREB and MCU will allow us to formulate novel epigenetic and molecular therapies that are likely to normalize maladaptive behaviors.

Keywords: pCREB, MCU, PAG, Opioid Withdrawal

Disclosure: Nothing to disclose.

W242. Deciphering Roles for Aberrant Histone Dopaminylation in Drug Addiction

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Background: Drug abuse is characterized by loss of control over drug intake, as well as persistent drug-seeking behaviors, despite negative consequences to both the drug abuser and those directly affected by their behavior. Given that drug addicts continue to crave and pursue drugs of abuse following extended periods of abstinence and/or treatment indicates that life-long changes in brain may occur to promote these behavioral phenotypes. Persistent changes in neuronal gene expression are known to promote physiological alterations implicated in drug addiction. More recently, cell-type and brain region specific epigenetic mechanisms have also been demonstrated to regulate transcriptional programs contributing to addictive-like behaviors; however, our understanding of how these mechanisms mediate life-long addiction remains limited.

Methods: Here, we employ a wide array of biochemical, biophysical (e.g., isothermal titration calorimetry, X-ray crystallography), molecular (e.g., ChIP, RNA-seq), physiological (e.g., fast-scan cyclic voltammetry) and behavioral approaches in a well established male rat model of cocaine self-administration (extended vs. restricted access, vs. non-reinforcement saline controls) to examine the impact of accumulating histone dopaminylation (vide infra) in ventral tegmental area (VTA) in response to cocaine (typical $n = 10$-20/group, one-/two-way ANOVAs and two-tailed student's t-tests were employed depending on selected comparisons). We affirm that all experimental protocols in animal studies were approved by the Institutional Animal Care and Use Committee at the ISMMS and were conducted in accordance with the National

Institutes of Health Guide for the Care and Use of Laboratory Animals

Results: Dopaminergic neurotransmission in the central nervous system plays a critical role in psychostimulant-induced neural plasticity, with alterations in dopamine production/function being implicated in both the development and treatment of substance use disorders. Although packaging of dopamine by the vesicular monoamine transporter is essential for numerous aspects of reward, recent data have demonstrated the additional presence of 'reserve' pools of extravesicular monoamines in the nucleus of monoamine producing neurons. Dopamine, as well as other monoamines, has previously been shown to form covalent bonds with certain cytoplasmic proteins catalyzed by the tissue Transglutaminase 2 enzyme. Our laboratory has recently identified histone proteins as robust substrates for dopaminylation in vivo, specifically on histone 3 glutamine 5 (H3Q5dop). In addition, our data demonstrate that chronic withdrawal from volitional administration of extended access cocaine (vs. forced administration – e.g., yoked controls or experimenter administered drug) in rodents results in high levels of dopamine accumulation in the nucleus of dopamine producing neurons in VTA, and a robust increase in histone dopaminylation (> 3 fold). Furthermore, we have demonstrated that inhibiting dopaminylation in VTA–which, in turn, attenuates cocaine-induced increases in striatal dopamine release dynamics via de-repression of VTA Drd2 expression–is sufficient to block cocaine-seeking behaviors following periods of extended withdrawal (> 50% reduction) without impairing reinforcement by nature rewards (e.g., food).

Conclusions: Taken together, these studies aid in our understanding as to how monoamines, specifically dopamine, function in brain to regulate neurotransmission-independent neuronal plasticity and drug-mediated behaviors.

Keywords: Epigenetics, Dopamine, Cocaine Addiction, Histone

Disclosure: Nothing to disclose.

W243. Accumbens Core GluN2B-Containing NMDA Receptors Mediate Rapid, Transient Synaptic Plasticity During Cue-Induced Nicotine Relapse

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Background: Nicotine addiction remains a significant public health liability and has been associated with long lasting changes in brain synaptic physiology within the basal ganglia that might contribute to relapse. Specifically, initiation of cue-induced nicotine seeking produces rapid, transient synaptic potentiation (t-SP) in nucleus accubmens core (NAcore) medium spiny neurons (MSNs), defined as increases in spine head diameter and AMPA to NMDA current ratios (A/N). The neural mechanisms that gate nicotine relapse-associated t-SP, however, remain largely unknown. Importantly, GluN2B-containing NMDA receptors within the NAcore traffic to the membrane and reemerge following withdrawal from nicotine, indicative of a subunit switch and possibly a return to developmental conditions where the brain is rendered more plastic. This upregulation renders cells within the NAcore hypersensitive and more plastic in response to the increased glutamatergic tone associated with cue-induced nicotine relapse. We have previously shown that systemic administration of a GluN2B antagonist, ifenprodil, decreases nicotine seeking, however it is unknown if (1) inhibition of these receptors within the NAcore specifically is relevant for inhibiting nicotine seeking, and (2) if GluN2B-containing NMDA receptors within the NAcore gate t-SP during nicotine relapse. Here we determined if pharmacological blockade as well as GluN2B-specific knockdown directly in the NAcore would prevent structural and functional t-SP associated with cue-induced nicotine relapse.

Methods: Male Sprague-Dawley rats (7-8 per group; 250-300 g) were single housed upon arrival. Following 7 days of acclimation, animals were implanted with intravenous jugular vein catheters as well as intracranial cannulae into the NAcore (A/P: + 1.5; M/L: + 2.0; D/V: -5.0). Following recovery, rats underwent one overnight food training session. Animals then began 2-hr nicotine self-administration sessions, where the active lever yielded one intravenous nicotine infusion (0.02 mg/kg/infusion) paired with a compound stimulus (discrete cue lights + tone). Acquisition criteria were > 10 infusions per day for 10 days. Following nicotine self-administration, rats were placed into daily extinction sessions (no nicotine or cues were delivered upon a lever press) for 14 days. On day 15, rats received intra-NAcore injections of ifenprodil (10 pmol) or vehicle, 15 minutes prior to a 15-minute (T (time) = 15) cue-induced reinstatement session. Rats were then sacrificed using an overdose of ketamine and xylazine. Perfusions were conducted, and brains were removed post-fixation. Slices of 200 um were made and a gene gun was used to label the fixed sections with DiI (1,1-dioctadecyl-3,3,3',3',-tetramethylindocarbocyanine perchlorate). Tissue was mounted, and high-resolution confocal microscopy was used to analyze MSN morphology within the NAcore.

Results: Contingent presentation of nicotine-conditioned cues elicited both nicotine seeking behavior and rapid increases in spine head diameter in vehicle-treated animals at T = 15. In contrast, intra-NAcore ifenprodil inhibited both cue-induced nicotine seeking and structural t-SP (measured via dendritic spine morphology) at this timepoint ($F(5,51) = 5.70$, $p < 0.001$). Specifically, GluN2B antagonism produced a significant leftward shift in the distribution of spine head diameter, indicating that acute administration of intra-NAcore ifenprodil was associated with a larger proportion of smaller spine head diameters in the NAcore ($F(1,30) = 12.77$, $p < 0.01$). However, no alterations in spine density were observed ($p > 0.05$).

Conclusions: These results indicate that NAcore GluN2B-containing NMDA receptors gate rapid, cue-evoked morphological plasticity which may contribute to relapse to nicotine use. While the current study partially links GluN2B-containing receptors to nicotine relapse-induced synaptic potentiation, ongoing studies in our laboratory are using siRNAs to specifically knockdown NMDA receptor subtypes within the NAcore. These current studies will elucidate further mechanisms involving the role of these receptors in nicotine relapse-associated t-SP. Specifically, GluN2A and GluN2B-specific siRNAs are currently being used to knockdown NMDA receptors previously found to be upregulated during nicotine withdrawal. MSN morphology and A/N are currently being measured at T = 15. Preliminary data show that the siRNA for the GluN2B subunit is successful in knocking down only GluN2B expression within the NAcore. Additionally, we have shown that the glial glutamate transporter (GLT-1) is down-regulated during nicotine withdrawal, and cue-induced nicotine reinstatement rapidly upregulates this transporter at T = 15. Interestingly, these preliminary studies suggest that treatment with the GluN2B-specific siRNA decreases GLT-1 expression at this timepoint. Thus, we hypothesize that knockdown of GluN2B-containing NMDA receptors during nicotine withdrawal may prevent the rapid upregulation of NAcore GLT-1 as well as t-SP during nicotine relapse. Taken together, these results show a potentially important neuron-glial interaction relevant to nicotine relapse motivation.

Keywords: NMDA Glutamate Receptors, Nicotine Addiction, Synaptic Plasticity, Nucleus Accumbens

Disclosure: Nothing to disclose.

W244. Use of TRAP to Identify Morphine-Induced Changes in Gene Expression in Ventral Tegmental Area Dopamine Neurons

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Background: Despite the prevalent long-term use and abuse of opiate drugs, relatively little is known about the neuroadaptations that occur with chronic use. We previously determined that chronic opiate exposure in mice and humans decreases the soma size of dopamine (DA) neurons in the ventral tegmental area (VTA), a key structure in the mesocorticolimbic reward circuit (Mazei-Robison et al., 2011). Importantly, the structural effects of chronic opioids appear to be drug-class specific, suggesting distinct molecular changes drive opioid-induced plasticity in the VTA. Consistent with this idea, in an RNAsequencing (RNAseq) screen we identified different patterns of gene expression changes in the VTA following morphine vs. cocaine treatment (Heller et al., 2015). However, previous large-scale screening studies for chronic opioid-induced changes in gene expression have been constrained to homogenates of the entire VTA, thus limiting the ability to identify molecular mediators specific to DA neurons. Therefore, this study addressed this knowledge gap by using translating ribosome affinity purification (TRAP) to isolate actively translating mRNA specifically from VTA DA neurons in the context of opiate exposure.

Methods: All experiments were approved by the Michigan State University IACUC and adhered to the Guide for the Care and Use of Laboratory Animals of the NIH. All experimental animals had ad libitum access to standard chow and water and were kept on a 12-hr. light-dark cycle. DA-specific Cre-driver lines (tyrosine hydroxylase (TH)-Cre and dopamine transporter (DAT)-Cre) or vesicular GABA transporter (vGAT)-Cre mice were crossed with Rosa26-L10a-eGFP mice. 10-wk old male and female mice were implanted s.c. with sham or morphine (25 mg) pellets under isoflurane anesthesia. TRAP purification was performed according to published protocols with the following minor alterations to isolate RNA from DA VTA neurons (Heiman et al., 2014). VTA was microdissected from coronal slices using a 14 G blunt needle and VTA from 4 mice were pooled for each immunoprecipitation (IP), and 4 biological replicates ($n = 16$ mice/group) were used for RNAseq analysis. RNA quantity and quality were assessed via Illumina Bioanalyzer, and all samples had RIN > 8 and RNA yields of > 10 ng. RNAseq was performed by the Univ. Maryland Institute for Genome Sciences. cDNA libraries were generated using a strand-specific library kit, samples were pooled (8 input and 8 IP) and RNA was sequenced across two lanes (Illumina HiSeq4000, 75 bp paired end read). Differential gene expression was assessed using edgeR/DEseq program and padj < 0.05 was considered significant. For RT-PCR validation, ~10 ng of RNA was reversed transcribed into cDNA and PCR was performed using SYBR green with samples run in triplicate and normalized to GAPDH using the ΔΔCt method. All RT-PCR statistical analyses were performed using GraphPad software and significance was set at $p < 0.05$.

Results: We crossed DA- and GABA-specific driver lines with Rosa26 EGFP-L10a mice, thereby allowing isolation of mRNA from VTA DA (DATEGFP-L10a) and GABA (vGAT EGFP-L10a) neurons. We first validated these models and found significant enrichment of TH and DAT mRNA and depletion of GABAergic markers (GAD and vGAT) in DATEGFP-L10a IPs and significant enrichment of GAD and vGAT and depletion of TH and DAT in vGAT EGFP-L10a samples, consistent with successful purification. We then completed RNA sequencing analysis on VTA samples from sham- and morphine-treated DATEGFP-L10a mice. We identified a similar number of differentially expressed genes in the input and IP fractions (~2000). However, there was little overlap between the two comparisons (< 10%) suggesting that morphine-induced changes in gene expression specific to VTA DA neurons are not evident in whole VTA analyses and that changes observed in whole VTA analyses may be driven by non-DA cells. This was the case for SGK1, a candidate gene whose expression is increased in the VTA by drugs of abuse: we find that this increase is not driven by increased expression in VTA DA neurons, and in fact, SGK1 mRNA seems to be depleted from DA neurons. We have now identified a number of novel morphine-regulated genes in both whole VTA and VTA DA neurons that we have validated by RT-PCR. These include genes in functionally relevant categories such as transcriptional regulation, cytoskeletal remodeling, neuronal activity, and neuropeptide signaling.

Conclusions: Using RNAseq, we were able to define the DA-specific transcriptome of both control and chronic morphine-treated DATL10a-GFP mice. We validated expression changes in previously identified morphine-regulated genes, such as SGK1 and Kcnab, as well as identified new candidate genes for chronic morphine-induced adaptations in VTA. Given the sparse overlap of morphine-regulated genes identified in RNAseq analyses of whole VTA vs. VTA DA neurons, this study highlights the importance of cell type-specific approaches to identify mechanisms that drive neuroadaptations in VTA DA neurons.

Keywords: Morphine, Ventral Tegmental Area (VTA), Dopamine, RNA Sequencing, Transcriptional Profiling

Disclosure: Nothing to disclose.

W245. Neuroinflammatory Nuclear Factor Kappa B Signaling in the Nucleus Accumbens Core Regulates the Effects of N-Acetylcysteine on Cue-Induced Nicotine Seeking and Glutamate Transporter 1 Expression

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Background: Withdrawal from chronic nicotine self-administration is associated with enduring alterations in glutamatergic plasticity within the nucleus accumbens core (NAcore), including basal potentiation of dendritic spines on medium spiny neurons and dysregulation of glial glutamate transport. The nuclear factor kappa B (NF-κB) pathway, which is activated by IκB kinase (IKK) and mediates drug-induced neuroinflammation, is a key regulator of synaptic plasticity and may be a critical regulator of cue-induced neurobehavioral plasticity. Notably, little is known about the role of NF- κB in cue-induced nicotine seeking. Here, we assessed whether 1) NF-κB mediates cue-induced nicotine reinstatement and 2) if NF-κB signaling underlies the attenuating effects of the antioxidant and glutamatergic agent N-acetylcysteine (NAC) on cued nicotine seeking.

Methods: Male Sprague-Dawley rats underwent nicotine self-administration (0.02 mg/kg/infusion) on a FR-1 schedule of reinforcement for a minimum of 10 days prior to 14 days of extinction training. On day 10 of extinction, rats received intra-NAcore microinjections of a herpes virus expressing constitutively active IKK (IKKca), a dominant negative mutant of IKK (IKKdn), or eGFP, as well as NAC (100 mg/kg/i.p.) or saline injections between days 10-14 of extinction. Following extinction, rats underwent cue-induced reinstatement (2 h) and were immediately sacrificed for NAcore tissue collection. Whole-cell lysates were assessed for GLT-1 protein expression. Phosphorylation of IκB kinase alpha (IκBα) was also assessed in NAC-naive rats to validate functional activity of the viral vectors. Two-way ANOVAs were used to examine

potential interaction effects between virus treatment and i.p. treatment at alpha = 0.05 significance level.

Results: IKKdn significantly suppressed phosphorylation of the inhibitory subunit of NF-κB, IκBα ($p < 0.05$). IKKdn blocked cue-induced nicotine reinstatement relative to extinction and IKKca impaired NAC from attenuating reinstatement ($p < 0.05$). Interestingly, IKKdn alone did not elevate glutamate transporter 1 (GLT-1) protein expression in the NAcore relative to IKKca. However, IKKca blocked NAC-mediated increases in GLT-1 expression relative to IKKdn-NAC treated rats.

Conclusions: These results indicate that NF-κB regulates cued nicotine seeking behavior and is a key mechanism underlying the therapeutic efficacy of NAC and its ability to restore GLT-1. Interestingly, these results also suggest that GLT-1-independent mechanisms may also underlie NAC's inhibitory effects over cue-induced drug seeking. These results highlight a novel target for the development of new pharmacotherapeutics that have anti-inflammatory activity and suppress nicotine relapse.

Keywords: Nicotine, Glutamate, GLT-1, Cue Reinstatement, Nuclear Factor Kappa B

Disclosure: Nothing to disclose.

W246. Targeting GSK3beta Signaling to Erase Cocaine Reward Memories

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Background: Compulsive drug-seeking and drug-taking behaviors are the hallmark of addiction, and these behaviors continue despite intense negative consequences to the individual. Maladaptive conditioned learning processes, together with molecular and cellular plasticity, play major roles in the development of this compulsive behavior. Addictive drugs including cocaine engage molecular signaling pathways that are involved in associative learning processes. Once learned, exposure to cues previously associated with cocaine can lead to conditioned physiological responses that are accompanied by intense drug craving, often triggering relapse. Hence, a goal of addiction treatment is to break the associations between previously learned positive subjective effects of cocaine and environmental cues that signal cocaine availability. In order to achieve this goal, detailed information is needed about the circuitry and molecular signaling within that circuitry that serves to reinforce and strengthen cocaine reward contextual memories. Glycogen synthase kinase-3beta (GSK3β) is uniquely positioned to regulate neuronal function and plasticity. We have previously shown that GSK3β activity is induced by and required for reconsolidation of cocaine reward memories. The present research sought to identify constituents of the signaling pathway and anatomical substrates involved in maintenance of cocaine reward memories, and to determine if targeting this signaling pathway could erase a cocaine mnemonic trace.

Methods: Using a place conditioning procedure, adult male mice were trained to associate a distinct context with cocaine (10 mg/kg) and subsequently displayed a preference for the cocaine-paired environment. Mice were re-exposed to the cocaine context in a drug-free state to reactivated cocaine reward memories. In some experiments, brains were obtained immediately following cocaine memory reactivation and brain regions of interest processed for protein measurements by Western blot analysis. In other experiments, pharmacological agents were administered after memory reactivation to test the ability of these agents to interfere with the reconsolidation process. Following pharmacological treatment, place preference was re-tested 24 h and 7 days later without further treatment or conditioning sessions. Control experiments progressed in a similar manner except without re-exposure to the cocaine context (ie, in the absence of memory reactivity). Both behavioral and protein data where analyzed by two-way ANOVA followed by Bonferonni's posthoc tests. N = 6-9.

Results: Reactivation of cocaine memories produced by re-exposure to the cocaine-paired context significantly increased GSK3β and mTORC1 activity in the nucleus accumbens, hippocampus and amygdala as compared with no re-exposure controls ($p < 0.05$). In order to determine their role in cocaine memory reconsolidation, inhibitors of GSK3β, namely SB216763, and mTORC1, rapamycin, were administered after memory recall and place preference was re-tested 24 h and one week later. Both SB216763 and rapamycin administered immediately following cocaine memory recall erased the previously established place preference ($p < 0.01$), suggesting that GSK3β and mTORC1 activity are necessary for reconsolidation to occur. Additional studies investigated the upstream mediators of this pathway. Given the importance of NMDA receptors in learning and memory processes, GluN2A- and GluN2B-containing NMDA receptors were investigated. NVP-AAM077 and ifenprodil both abolished an established cocaine place preference when administered after recall of the cocaine-place memory but were ineffective in the no re-exposure control groups. In addition, pretreatment with NVP-AAM077 or ifenprodil prior to re-exposure to the cocaine-pair environment prevented the activation of GSK3β in the accumbens, hippocampus, and amygdala.

Conclusions: Taken together, these results suggest that recall of cocaine reward memories triggers a signaling cascade originating with GluN2A- and GluN2B-NMDA receptors and resulting in activation of GSK3β and mTORC1. Activation of this pathway is required for reconsolidation of the cocaine mnemonic trace after retrieval. Results of this study demonstrate that it is possible to erase cocaine contextual memories by targeting the signaling pathway needed to maintain such memories, thus providing an opportunity for therapeutic intervention to help prevent cue induced relapse.

Keywords: Cocaine Seeking, Memory Reconsolidation, GSK3, NMDA Glutamate Receptors

Disclosure: Nothing to disclose.

W247. Poised Gene Expression of Nr4a1 and Nr4a1-Target Genes in Cocaine Addiction

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Background: A growing body of bioinformatics evidence supports the notion that chromatin modifications play a key role in drug addiction. Beyond regulation of the binary states of activated and repressed, genes also exist in a 'poised' state, in which they are silent but poised for immediate action. Poised genes are simultaneously enriched in two histone modifications, tri-methylated histone H3 lysine 4 (H3K4me3), a mark of active genes, and tri-methylated histone H3 lysine 27 (H3K27me3), which is repressive. The shift from bivalency to mutual exclusion is one mechanism by which H3K4me3 activates rapid gene expression, which is an intriguing mechanism in the context of addiction relapse. The immediate early gene, Nuclear Receptor Subfamily 4 (Nr4a), is functionally linked to reward signaling and is regulated by H3K4me3/H3K27me3 bivalency. Nr4a1 occupancy at target genes increases in response to dopamine, leading to recruitment of chromatin and DNA-modifying enzymes to regulate gene

expression. Intriguingly, Nr4a1 expression increases in response to drug exposure but returns to baseline following a period of abstinence, at which time Nr4a1 target genes are found to remain regulated. Given that chromatin modifications confer long-lasting changes in gene expression, histone modifications acquired during abstinence may cause individual genes to "remember" prior drug exposure, even in the absence of sustained changes in transcription. There is an inverse relationship between the enrichment of Nr4a1 and H3K27me3, at poised genes, both in culture and in brain reward areas, suggesting that Nr4a occupancy may promote the conversion from poised to active chromatin in order to regulate cocaine-mediated gene expression, physiology and behavior.

Methods: Intravenous self-administration was used to expose mice to cocaine and abstinence. Single-sample sequencing (S3EQ) was used to analyze global changes in chromatin bivalency (ChIP-seq) and transcription (RNA-seq). CRISPR/dCas9-mediated gene activation and repression were used to regulate Nr4a1 expression in vivo. Conditioned place preference was used to assess cocaine reward.

Results: To gain a comprehensive understanding of cocaine regulation of gene poising, we analyzed genome-wide changes in H3K4me3 and H3K27me3 in the nucleus accumbens (NAc) following cocaine self-administration. We discovered that volitional cocaine taking leads to a global reduction of H3K4me3/H3K27me3 chromatin bivalency in mouse NAc. An increase in the mutual exclusivity of these two modifications was driven primarily by enrichment of the activating modification, H3K4me3, in regions without concomitant increases in the repressive modification, H3K27me3. This phenomenon was observed at several genes relevant to dopaminergic regulation of drug addiction, including Nr4a1. In addition, transcriptomic analysis of the same mice found upregulation of Nr4a1 and dopaminergic target genes. To determine the causal relevance of Nr4a expression on downstream gene target regulation and reward behavior, we engineered CRISPR/dCas9-based transcription factors targeting Nr4a1; either dCas9-KRAB or -VP64, which mediate gene repression or activation, respectively. CRISPR-mediated gene regulation in NAc caused significant activation or repression of Nr4a1, and bidirectional modulation of Nr4a1-target gene expression. With respect to its role in dopaminergic gene regulation, we found that cocaine CPP was attenuated by CRISPR-mediated activation of Nr4a1 expression. Establishing the molecular basis for epigenetic drug memories will further our understanding of the chronic nature of drug abuse and addiction.

Conclusions: These findings show that volitional cocaine taking reduces global chromatin bivalency, leading to activation of gene expression relevant to cocaine reward behavior.

Keywords: CRISPR/dCas9, Cocaine Self-Administration, Chromatin

Disclosure: Nothing to disclose.

W248. Transient Chemogenetic Inhibition of Direct Pathway Neurons in the Dorsal Striatum Enhances Methamphetamine Addiction

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Background: The dorsal striatum is important for the development of drug addiction; however, the role of dopamine D1 receptor (D1R) expressing medium-sized spiny striatonigral (direct) pathway neurons (D1-MSNs) in regulating excessive methamphetamine intake remains elusive. It is therefore hypothesized that D1-MSNs in the dorsal striatum may contribute to reinforcing effects of methamphetamine and produce dependence-like behavior. Here we seek to determine if inhibiting D1-MSNs in the dorsal striatum alters methamphetamine self-administration.

Methods: A viral vector-mediated approach was used to overexpress the inhibitory (Gi coupled-hM4D) or stimulatory (Gs coupled-rM3D) designer receptors exclusively activated by designer drugs (DREADDs) engineered to only respond to exogenous ligand clozapine-N-oxide (CNO) selectively in D1-MSNs in the dorsal striatum.

Results: CNO treatment in animals overexpressing hM4D increased responding for methamphetamine compared to vehicle saline in a within subject treatment paradigm. CNO treatment in animals that did not express DREADDs (DREADD naïve-CNO) or expressed rM3D did not alter responding for methamphetamine, demonstrating specificity for hM4D-CNO interaction. Postmortem tissue analysis reveal that hM4D-CNO animals had reduced neuronal activation in the dorsal striatum compared to rM3D-CNO animals and DREADD naïve-CNO controls. Cellular mechanisms in the dorsal striatum associated with reduced neuronal activation and enhanced methamphetamine taking in hM4D-CNO animals reveal enhanced expression of D1R and protein kinase B (Akt), and reduced activation of $Ca2+$/calmodulin-dependent kinase II (CaMKII) compared to drug naïve controls and rM3D-CNO animals. Notably, rM3D-CNO animals had enhanced activity of extracellular signal-regulated kinase (ERK1/2), Akt and CaMKII in the dorsal striatum compared with hM4D-CNO animals.

Conclusions: Our studies indicate that transient inhibition of D1R expressing neurons-mediated strengthening of methamphetamine addiction-like behavior is associated with cellular adaptations that support dysfunctional dopamine signaling in the dorsal striatum.

Keywords: Long Access self-Administration, D1 Dopamine Receptors, Akt, MAPK, CaMKII

Disclosure: Nothing to disclose.

W249. Genome-Wide Methylation in Alcohol Use Disorder Subjects: Implications for the Cortico-Limbic Glucocorticoid Receptors (NR3C1) Expression

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Background: Alcohol is known for its acute anxiolytic effects mediated by its interaction with GABAA receptors (Olsen, 2018). However, chronic alcohol activates the hypothalamic-pituitary-adrenal axis and stimulates the release of glucocorticoids (Blaine and Sinha, 2017) - the primary mediators of the stress response. Glucocorticoids exert their action through specific receptors, i.e., the glucocorticoid receptor (encoded by NR3C1). The human NR3C1 gene is comprised of nine untranslated alternative first exons (1A-J) and eight translated exons (2 to 9). Seven of the exons 1 variants are embedded within a CpG island known to be susceptible to epigenetic regulation via DNA methylation (Daskalakis and Yehuda, 2014). These epigenetic changes have been associated with psychopathological conditions in adulthood (Palma-Gudiel et al., 2015). As of today, no detailed studies have reported changes in the brain transcriptome via DNA methylation of stress-related genes in alcohol use disorder (AUD) subjects. In the present study, using an updated microarray assay followed by

the identification of 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) by specific immunoassay, we have investigated whole genome DNA methylation patterns and more specifically the regulation of NR3C1 and stress-responsive gene expression in the prefrontal cortex (BA10) of AUD subjects.

Methods: Post-mortem brain samples were obtained from 25 controls and 25 AUD subjects from the New South Wales Tissue Resource Centre (University of Sydney, Australia). Genome-wide DNA methylation was assessed using an Infinium® MethylationEPICBeadChip microarray (Illumina), detecting methylation status at over 850,000 loci in the human genome. Statistical analysis of the microarray data was done in R (v 3.4.1) using the minfi package (v 1.22.1). Differential methylation per CpG was tested with the limma package (v 3.32.5). Functional analysis was assessed for loci with a nominal p-value < 0.0011. Gene Set Enrichment Analysis (GSEA; Broad Institute, USA) was used to calculate gene cluster enrichment. The enriched pathways were plotted as a cluster map based on their biological function using Cytoscape®. Gene ontology classification was assessed using the Panther Classification System. Canonical pathways and gene networks were analyzed by QIAGEN's Ingenuity® Pathway Analysis (IPA®, Qiagen). Network analysis was used to evaluate highly connected molecules from our list and the QIAGEN knowledge base with a size constraint of 35 focus molecules per network. Loci detected by the microarray were validated by methyl-DNA-immunoprecipitation and hydroxymethyl-DNA-immunoprecipitation assays using the MagMeDIP kit, as well as by chromatin immunoprecipitation. mRNA levels were determined by qRT-PCR. Protein determination was assessed by western blot.

Results: The genome-wide analyses performed in BA10 tissue of controls and AUD subjects showed 1337 differentially methylated CpGs in AUD subjects, 597 hypomethylated and 740 hypermethylated (pnominal < 0.005). Mapping of gene clustering based on their biological function allowed the visualization of enriched categories, such as 'response to stimulus' and 'immune response' in our cohort. A large number of pathways sharing genes involved in 'response to stress' were detected, among which genes involved in 'response to alcohol' were the most enriched in AUD subjects. Panther GO showed several processes of relevance for both alcohol use disorders and stress. Of note, we found that 40% of genes enriched in 'response to stimulus' were involved in 'response to stress'. IPA® canonical pathway analysis also indicated bias towards addiction and stress, e.g., 'CREB signaling in neurons', 'corticotropin releasing hormone signaling'. The network analysis revealed a top network involved in drug metabolism. The hierarchical clustering of this network indicates a central regulatory role for NR3C1.

We found that chronic exposure of adult subjects to large doses of alcohol results in a significant increased methylation of the NR3C1 exon variant 1 H, with a particular increase of 5hmC over 5mC. This imbalance might be responsible for reduced MECP2 binding. The hypermethylation of NR3C1 induced by chronic alcohol consumption is different from the increased methylation of the 1 F exon variant reported in suicidal patients with a history of child abuse (McGowan et al., 2009). Changes in chromatin remodeling at the NR3C1 exon 1 H were associated with significantly reduced NR3C1 mRNA levels in BA10, hippocampus, amygdala and striatum of AUD subjects. These changes were associated with reduced expression of NR3C11H in BA10 and the hippocampus of AUD subjects. In BA10, protein levels of NR3C1 were reduced in AUD subjects in both cytosolic and nuclear fractions. In addition, we found that the expression of several NR3C1 chaperones and stress-responsive genes (e.g., FKBP5, CRF, POMC) is altered in the BA10 and hippocampus of AUD subjects. Of note, a significant correlation between CRF mRNA levels and ethanol daily use (g) was detected in BA10 and hippocampus.

Conclusions: The present work suggests that alcohol-dependent epigenetic regulation of NR3C1 and other stress-related genes in specific stress/reward-responsive brain regions might be involved in the pathophysiology of AUD (supported by the P50AA022538 NIAAA-NIH grant to SCP and AG).

Keywords: DNA Methylation, Glucocorticoid Receptor, Alcohol Use Disorders

Disclosure: Nothing to disclose.

W250. No Increase in Chronic Pain Among Opioid-Dependent individuals Randomized to Treatment With Extended-Release Naltrexone or Buprenorphine-Naloxone

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Background: Data are inconsistent on whether treatment with an opioid receptor blocker such as extended-release naltrexone might induce pain or aggravate existing pain among opioid dependent individuals.

Methods: A prospective open label clinical study where 157 opioid dependent adults with no other serious mental or somatic disease were randomized to 12 weeks treatment with either long-acting naltrexone or buprenorphine-naloxone (BP-NLX), followed by nine months open treatment study with either drug of participant's choice. Participants of both genders aged 18-60 years were recruited at outpatient addiction clinics at five urban hospitals in Norway.

Extended-release naltrexone was administered as an intramuscular injection (380 mg) every four weeks or oral-buprenorphine-naloxone given daily in flexible 4-16 mg doses.

Changes in pain assessed every 4 weeks using the Norwegian Short-Form of McGill Pain Questionnaire (NSF-MPQ).

Results: Participants in either treatment group reported no increase in sensory pain, affective pain, or present pain intensity on the McGill Pain Questionnaire including the subgroups of participants with chronic pain. Also, participants switching from buprenorphine-naloxone to extended-release naltrexone treatment after week 12 reported no increase in pain intensity during longer term treatment. Women experienced more affective pain symptoms than men ($p = 0.01$).

Conclusions: Switching from daily opioid use or opioid treatment (ART) to opioid receptor blocking long-acting naltrexone did not induce pain or aggravate mild to moderate chronic pain in opioid-dependent individuals. The results indicated no analgesic effects of opioids on chronic pain in this cohort of individuals.

Keywords: Opioid Dependence, Chronic Pain, Extended-Release Naltrexone, Buprenorphine-Naloxone

Disclosure: Nothing to disclose.

W251. Placebo-Controlled Randomized Clinical Trial Testing the Efficacy and Safety of Varenicline for Smokers With HIV

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Background: People living with HIV/AIDS (PLWHA) smoke tobacco at higher rates and have more difficulty quitting than the general population, which contributes to significant life-years

lost. The effectiveness of varenicline, one of the most effective tobacco dependence treatments, is understudied in HIV. The objective of the current study was to evaluate the safety and efficacy of varenicline for smoking cessation among PLWHA.

Methods: This was a single-site, randomized, double-blind, placebo-controlled, phase 3 clinical trial. We screened 748 individuals and 179 were randomized to treatment. Participants were PLWHA on antiretroviral therapy who were treatment-seeking daily smokers. Smokers were randomized (1:1) to 12 weeks of varenicline (n = 89) or placebo (n = 90). All participants received six smoking cessation behavioral counseling sessions. The primary outcome was 7-day point prevalence abstinence, confirmed with breath carbon monoxide, at Weeks 12, 18, and 24. Continuous abstinence and time to relapse were secondary outcomes. Safety measures were treatment-related side effects, adverse events, and blood pressure, viral load, and antiretroviral (ART) adherence.

Results: Of the 179 smokers, 81% were African American and 68% were male. Varenicline increased cessation at Week 12 (28.1% vs. 12.1%; OR = 4.54, 95% CI 1.83-11.25, P < .05) and Week 18 (21.3% vs. 11.1%; OR = 3.12, 95% CI 1.22-7.97, P < .05). Continuous abstinence from Week 9 to Weeks 12 and 18 were higher for varenicline vs. placebo (Ps < .05); at Week 24, there was no effect of varenicline for point prevalence or continuous abstinence (Ps > .05). Varenicline delayed time to relapse (B = .19 [95% CI 2.81-43.1], P < .05). There were no differences between varenicline and placebo on safety measures (Ps > .05).

Conclusions: The overall findings indicate that use of varenicline, with behavioral counseling, is safe and effective for smokers with HIV. Varenicline was not associated adverse outcomes, including cardiovascular and psychiatric events, and significantly increased quit rates at the end of treatment and out until 6 weeks following treatment cessation. These results provide important information for both patients and clinicians as they engage in efforts to address smoking among PLWHA and improve their quality and quantity of life.

Keywords: Tobacco Smoking, HIV, Smoking Cessation

Disclosure: Nothing to disclose.

W252. Effects of Extended Cannabis Abstinence on Symptoms and Cognition in Major Depression: Preliminary Findings

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Background: Background: Major depression is a widespread mental health problem with a lifetime prevalence of ~15%. Heavy cannabis use has been shown to be associated with worsening of mood symptoms in Major Depressive Disorder (MDD). However, the prospective association between MDD and cannabis use has not been well-studied. The present study assesses the effects of a 28-day abstinence period in patients with Cannabis Use Disorder (CUD) and MDD. Our goal is to determine the effects of 28 days of cannabis abstinence on mood symptoms and cognition in people with co-occurring CUD and MDD.

Methods: Methods: Participants between the ages of 18 and 55 with comorbid CUD and MDD were asked to remain abstinent from cannabis for a 28-day period. Subjects who achieved biochemically-verified abstinence (THC-COOH urine levels < 20 ng/ml at Day 28) were given a contingent bonus of $300. Mood was assessed with the Hamilton Depression Rating Scale (HDRS-17), anxiety with the Beck Anxiety Inventory (BAI), and anhedonia was assessed using the Snaith-Hamilton Pleasure Scale (SHAPS).

Results: Results: To date, we have recruited 5 subjects with co-occurring MDD and CUD, with a mean age of 33.7 + /-16.0 years, mean baseline HDRS-17 scores of 17.0 + /-4.6 and mean WTAR IQ Scores of 103 + /-9. Of the three study completers to date, two subjects achieved endpoint cannabis abstinence. Overall, there was a modest mean decrease (~20%) in HDRS-17 and BAI scores across the 28 day. Moreover, there were large reductions (> 50%) in anhedonia scores on the SHAPS.

Conclusions: Conclusion: While preliminary, our initial results suggest that cannabis abstinence is associated with improvements in mood, anxiety and anhedonia symptoms in cannabis-dependent patients with MDD. Data from the on-going study will be presented.

Supported in part by funds from the Astrid H. Flaska Foundation/Scotiabank through the CAMH Foundation, and NIDA grant R21-DA-043949 to Dr. George.

Keywords: Cannabis Use Disorder, Major Depression Disorder, Abstinence, Anhedonia

Disclosure: Nothing to disclose.

W253. Fatal Overdose in Recently Detoxified HIV-Positive Persons With Opioid Use Disorders: The Role of Naltrexone in Prevention

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Background: Persons with opioid use disorders have an increased risk of fatal overdose. Concerns have been expressed that naltrexone treatment increases this risk due to adherence problems and increased sensitivity to opioid effects, but few data are available to confirm or deny these concerns.

Methods: Overdoses are compared from two studies, both done in St. Petersburg, Russia at the same time by the same group of investigators. One enrolled 349 detoxified, opioid addicted, HIV + patients and randomized them to a 6-month case management intervention or usual care with followup for 12 months to assess linkage to HIV care and HIV outcomes. The other enrolled 200 patients with similar demographic features and randomized them to a 12-month course of daily oral naltrexone placebo and a naltrexone implant that blocks opioids for 3 months, or to oral naltrexone 50 mg/day and a placebo implant. Number of deaths, overdose related deaths, percent receiving antiretroviral therapy (ART), and percent in outpatient addiction treatment at 12-months were assessed.

Results: Patients in each study had a mean age of 33 years, 74% were male, 48% were unemployed, over 90% positive for HCV, and 16% had overdosed. All 12-month followups favored the group that received naltrexone: 88.4% vs 25.7% on ART; 67.5% vs. 13% in outpatient addiction treatment; 5.2% vs 13.5% deaths; and 1.5% vs 7.3% overdose deaths. All differences were significant except number of deaths.

Conclusions: Patients in the naltrexone study had fewer overdose deaths and more adherence to ART and addiction treatment than those in the study that did not offer naltrexone. Though not a randomized trial, the similarity in demographic features between the groups and the fact that the studies were done at the same time, in the same city and by the same investigators, suggests that starting HIV +, opioid addicted patients on naltrexone in a setting where agonist treatment is not available reduces the risk of overdose death and improves addiction and HIV treatment outcomes.

Keywords: Extended-Release Naltrexone, Naltrexone, Opioid Overdose

Disclosure: Nothing to disclose.

W254. Neuroscience Factors Predicting Latent Classes of Individuals Across the Spectrum of Alcohol Use and Misuse

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Background: Addictions Neuroclinical Assessment (ANA), which focuses on three neuroscience domains with relevance for addiction: Incentive Salience, Negative Emotionality, and Executive Function. Assessments of these domains are currently being collected as part of a long-term ongoing screening and natural history protocol (SNHP), which collects data on individuals across the spectrum of alcohol use and misuse, including those with alcohol addiction. The current inquiry builds on a previous factor analysis of measures collected within this SNHP and which mapped onto the three ANA neuroscience domains. In this analysis, we used the measures as predictors of latent classes among our participant sample to determine how well these neuroscience-related measures may predict heterogeneity within our participants.

Methods: Participants included individuals seeking treatment for addiction to alcohol at the NIAAA treatment center in Bethesda, MD, USA, and individuals screened in the NIAAA outpatient clinic for participation in other research studies, between 2014 and 2016. Demographic data and psychiatric diagnoses obtained from the Structured Clinical Interview for DSM-IV were collected, as well as the following measures for analysis, organized by ANA neuroscience domain: Executive Function: Adult Self-Report Scale for ADHD (ASRS/ADHD); Barratt Impulsiveness Scale (BIS); Delay Discounting; NEO-Personality Inventory-Revised (NEO); UPPS Impulsive Behavior Scale (UPPS); Negative Emotionality: Montgomery-Asberg Depression Rating Scale (MADRS); Spielberger Trait Anxiety; Buss Perry Aggression scale; and Incentive Salience: four specific questions from the Obsessive Compulsive Drinking Scale (OCDS) and the Alcohol Dependence Scale (ADS) that focus specifically on thoughts and desires to consume alcohol. We conducted stepwise Latent Class Analysis (LCA), using the above measures as predictors, with demographic variables as covariates and the number of heavy drinking days and average drinks per drinking day from the 90-day Timeline Followback (TLFB) as the distal outcome measure. Model fit was evaluated using a combination of Bayesian Information Criterion (BIC, Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (LRT) and Lo-Mendell-Rubin Adjusted LRT, as well as theoretical considerations. All data analyses were conducted using Mplus.

Results: The sample included 454 participants (41% female, 41% Caucasian). Of these individuals, approximately 47% were diagnosed with either alcohol abuse or dependence (43% alcohol dependence, 4% alcohol abuse). The average age of the sample was 40.28 years (SD = 13.5) and the mean years of education was 14.7 (SD = 3.57). Taking into account the various assessments of model fit, both the statistical and theoretical considerations suggested that a two-class solution best fit the data. Class 1, including 65.2% of the sample (n = 296), comprised individuals with lower scores of all forms of impulsivity, aggression, neuroticism, urgency, depression, anxiety, ADHD symptoms, and craving for alcohol, and higher levels of agreeableness and conscientiousness, than individuals in Class 2. Class 2 comprised 34.8% of the sample (n = 158) and had a significantly higher proportion of men than Class 1. The two classes differed significantly on drinking measures, as well, with Class 2 drinking both more average drinks per drinking day ($2 = 259.63$, $p < 0.0001$) and total heavy drinking days ($2 = 404.60$, $p < 0.0001$).

Conclusions: Our analyses identified a two-class solution as the best fit, based on statistical and theoretical criteria. Given the differences in drinking variables between these classes, we found that heavier drinking, as measured in both frequency and quantity, is associated with higher levels of impulsivity, negative affect, and executive dysfunction. Further analyses of this sample might explore whether these variables meaningfully distinguish between individuals diagnosed with alcohol dependence, i.e., whether they contribute to an understanding of the heterogeneity within AUD. Further data collection of assessments targeted towards the ANA neuroscience domains will allow us to explore their contribution to heterogeneity in greater depth, while this inquiry serves as a critical starting point for that line of inquiry.

Keywords: Alcohol, Cognitive Neuroscience, Latent Class Analysis

Disclosure: Nothing to disclose.

W255. Nicotine Effects on Dependence-Related Associative Learning in Human Non-Smokers

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Background: Tobacco smoking is the most common preventable cause of death in the US. Nicotine is considered the primary constituent responsible for tobacco addiction. Given its relatively weak primary reinforcing effects, its high abuse potential is paradoxical, possibly reflecting the behavioral control exerted by drug-associated cues. Cue-controlled behavior appears to play a larger role for tobacco dependence than for any other abused drug. We tested a potential explanation, hypothesizing that nicotine enhances associative learning, the mechanism underlying the conditioning of drug-associated stimuli.

Methods: On two separate days, 32 non-smokers were administered a transdermal nicotine patch (7 mg/24 h) and a placebo patch in a double-blind cross-over study. After a 5-hour absorption period, participants were tested with two behavioral paradigms designed to isolate incidental stimulus-stimulus or stimulus-response learning. Repeat testing across the two test days was enabled by two task versions, each with a unique stimulus set.

The stop signal task required speeded gender judgments of face stimuli. In 24% of trials, presented unpredictably, a tone signaled that the response should be withheld. The stop-signal delay (SSD) between the onset of the face stimulus and the presentation of the tone varied from trial to trial as a function of whether or not a response was successfully withheld. Unbeknownst to participants, some faces were always paired with stop trials.

The Conditional Associative Learning (CAL) task required feedback-based learning of associations between pairs of shape stimuli. Five pairs were made from either ten unique stimuli (Unique Task), or from different combinations of two identical sets of five stimuli, with correct associations depending on contextual information (Crossed Task).

Results: In the stop signal task, stop-responses were facilitated over time to stimuli paired with stop trials relative to stimuli not systematically paired with stop or go trials, as indicated by longer SSDs. When previously stop-associated stimuli were paired with

go trials, go-responses were slowed relative to stimuli not systematically paired with stop or go trials. Nicotine significantly enhanced the facilitation of stop-responses to stimuli paired with stop trials, and the slowing of go-responses to stimuli previously paired with stop trials. Both findings indicate stronger associations between paired stimuli and the stop signal/stop response.

In the CAL Unique and Crossed Tasks, nicotine had no effects on the decline in errors over time when participants purposefully endeavored to learn which stimuli belonged together. However, in the Crossed Task, nicotine specifically increased the incorrect choice of stimuli that were associated with the test stimulus in a different context, indicating stronger stimulus-stimulus associations at the expense of flexible context-adaptive behavior.

Conclusions: The results indicate that nicotine can enhance incidental associative learning. Stronger associations at the expense of flexible context-adaptive behavior mimics the behavioral control exerted by drug-associated stimuli, which is thought to unfold in an automatized manner at the expense of frontoexecutive evaluative control. By promoting the formation of smoking-associated stimuli and habitual, cue-controlled drug-taking, this mechanism may explain nicotine's paradoxically high abuse potential.

This work was funded by R03 DA037509 (B. Hahn).

Keywords: Nicotine, Associative Learning, Dependence

Disclosure: Nothing to disclose.

W256. Aberrant Neurocircuitry Underlying Mentalizing and Social Cognition in Cocaine Use Disorder

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Background: Mentalizing (the ability to understand the mental states of others) is a social cognitive function crucial for adaptive social functioning. Individuals with cocaine use disorders (iCUD) show multiple social cognition deficits, spanning the domains of social reward processing and moral judgment, and thereby may exhibit alterations in mentalizing behavior and underlying circuitry, but this suggestion has not been tested. We hypothesized that, during an fMRI task of mentalizing, iCUD would show behavioral impairments in conjunction with altered engagement of the mentalizing network, comprising the prefrontal cortex, superior temporal sulcus, temporoparietal junction, temporal pole; regions similarly implicated in the pathophysiology of drug addiction.

Methods: We examined differences in mentalizing and its neural correlates between 15 iCUD and 15 healthy controls (HC), matched on gender, race, grade-equivalent cognitive performance and verbal IQ, but not on age (iCUD > HC), which was covaried in the analyses. Participants performed the fMRI Why/How Localizer task, previously validated to probe the mentalizing network in an independent healthy community sample. The task presented photographs of naturalistic human behaviors (spotlighting Faces versus Hands) and asked participants to respond about How versus Why these behaviors are being performed (2×2 task design). Whole-brain analyses were conducted using a 2 (group) × 4 (condition) full factorial model; significance was set at a height threshold of punc. < .001 and a cluster extent threshold of 20 voxels. We additionally conducted regions of interest (ROI) analyses, using a priori defined 10 mm spheres centered at the peak coordinates of regions showing activation of the Why > How contrasts in the previous community sample.

Results: The groups did not differ in task performance (accuracy or reaction time), and therefore the neural activation differences between the groups cannot be attributed to differences in behavior. As expected, the task activated a wide spectrum of regions comprising the mentalizing network across all conditions and groups. The omnibus Group × Condition interaction was not detected at a whole-brain corrected threshold. Instead, significant main effects of group (i.e., across task conditions) were observed in multiple frontal, temporal, parietal and occipital cortical regions. Specifically, compared to HC, iCUD showed greater overall activity in the right precuneus [x = 17, y = -61, z = 24, Brodmann Area (BA) = 31; Z-peak = 6.64 cluster-level pFWE-cor. < .001, k = 34 voxels], and reduced activity in the right dorsolateral prefrontal cortex (x = 50, y = 30, z = 18, BA = 9; Z-peak = 5.59 cluster-level pFWE-cor. < .001, k = 38 voxels) and the right superior motor cortex (x = 2, y = 6, z = 57, BA = 6; Z-peak = 5.28 cluster-level pFWE-cor. < .001, k = 66 voxels). A condition main effect (Why > How, across study groups) was observed in the left medial superior frontal gyrus (x = -2, y = 51, z = 33, BA = 9; Z-peak-value = 4.4, cluster-level pFWE-cor. < .001, k = 51 voxels). Beyond the whole-brain effects, ROI analyses revealed a group main effect in the right anterior superior temporal sulcus (x = 54, y = 0, z = -28, BA = 21; HC > iCUD; p = .019). Among the iCUD group, activation during the Why condition in the temporal sulcus (BA = 21) correlated negatively with severity of cocaine dependence (rs = -.762, p < .001), where the greater the severity of cocaine dependence, the less the activation in this brain region.

Conclusions: For the first time in addiction, we examined the neural underpinnings of mentalizing, an important component of social cognition whereby individuals infer intentions underlying the behavior of others. We found that the Why/How task engaged activations in regions previously implicated in mentalizing, including those in the visual and attention networks as well as the default network, providing validity for its first use in a patient-population (iCUD). Despite absence of differences in task performance (perhaps because this version of the task was not particularly difficult), abnormalities in neural processing during mentalizing nonetheless were observed, such that in iCUD compared with HC there was a greater engagement of a region implicated in exteroceptive processes (BA 31) and reduced engagement of regions implicated in social perception (BA 21), behavioral monitoring (BA 9) and mental operation (BA 6). Future efforts could be directed at testing whether mentalizing impairments may exacerbate illness severity, promote relapse and impact treatment outcome in iCUD and other addictions. If so, then developing interventions, for example via mentalization-based treatments (which have proven efficacy for enhancing social cognition in other psychiatric patients) that incorporate addiction-related facets, may prove efficacious in normalizing the neural underpinnings of social cognition and improving outcomes.

Keywords: Cocaine Addiction, Social Cognition, fMRI, Mentalizing

Disclosure: Nothing to disclose.

W257. Effects of Cocaine Use on Emotion Recognition: A Potential Role for Recency of Drug Use and Long-Term Abstinence

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Background: Determining the neuropsychological capacity for recognizing emotions in addicted populations is critical given that impairments may contribute to real-life social dysfunction, such as troubled interpersonal relationships and decreased social networks. To date, studies examining the effects of cocaine addiction on emotion recognition performance have yielded inconsistent findings. While some investigations show that cocaine addiction is associated with enhanced ability to identify emotions, other studies demonstrate impairment with use. Inconsistencies may be due to varying lengths of abstinence given that social-cognitive function may vary with recency of use. Therefore, we investigated the effects of duration of cocaine abstinence on emotion recognition and social functioning in individuals with cocaine use disorder (CUD). Moreover, given that cocaine users exhibit marked structural alterations in brain regions that are crucially involved in orchestrating social-cognitive functions (e.g., amygdala, orbitofrontal cortex, insula), we also explored whether regional gray matter volume (GMV) was associated with emotion recognition performance as a function of recency of use.

Methods: Performance on the Emotion Recognition Task from the Cambridge Neuropsychological Test Automated Battery (CANTAB) was compared between current cocaine users (CUD+, n = 30; cocaine-positive urine), short-term abstainers (CUD−ST, n = 26; abstinence < 6-months), long-term abstainers (CUD-LT, n = 21; abstinence ≥ 6-months) and healthy controls (n = 46). Self-reported social functioning was assessed using the family-social subscale from the Addiction Severity Index (ASI). GMV was indexed in a subset of the sample (total N = 73: CUD+, n = 14; CUD-ST, n = 16; CUD-LT, n = 16; Control, n = 27) using voxel-based-morphometry (VBM) applied to structural T1-weighted images using a 3D MPRAGE sequence. Age and total intracranial volume were controlled for in all VBM analyses.

Results: Results revealed that CUD+ had greater difficulties recognizing happiness, sadness and fear compared to controls ($p < 0.01$). A similar pattern was observed in CUD-ST for fear ($p < 0.01$). Further, CUD+ showed compromised social function in comparison to CUD-LT and controls as measured by the ASI [e.g., spending most time alone and having greater interviewer severity ratings for social function than CUD-LT ($p = 0.03$) and CTL ($p = < 0.01$)]. Whole brain analysis showed reduced GMV in the right amygdala and bilateral cerebellum in CUD+ compared to CUD-LT and CTL (pFWE-corr < 0.05). In addition, collapsed across all subgroups, a region of interest analysis revealed that greater GMV in the bilateral cerebellum was associated with better recognition for happiness ($p < 0.05$). Relationships between social functioning outcomes and GMV were not observed.

Conclusions: Our findings demonstrate that emotion recognition is impaired in CUD+, and that selective deficits (in fear) may persist with up to 6 months of abstinence. Notably, reduced GMV in the cerebellum may specifically underlie deficits in identifying positive emotion in CUD+. Encouragingly, recovery of emotion recognition performance and GMV of the amygdala and cerebellum may be feasible with extended abstinence. Targeting emotion recognition deficits with specialized interventions (e.g., social skills training) may strengthen social connections including interpersonal and therapeutic relationships and thereby enhance the likelihood for individuals with CUD to achieve long-term abstinence and successful recovery.

Keywords: Cocaine Addiction, Social Cognition, Emotion Recognition, Voxel-Based Morphometry (VBM), Abstinence

Disclosure: Nothing to disclose.

W258. Contributions of Childhood Trauma and Current Perceived Stress to Risk for Alcohol Use, Anxiety, and Mood Disorders: A Multi-Group Path Analysis Model

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Background: Childhood trauma has been linked to a number of adverse consequences in adulthood including alcohol and other substance use disorders. While there is extensive evidence that exposure to early life stress can have long-lasting effects on health and behavior, such outcomes are also influenced by stress levels experienced at the time the outcomes are measured, typically in adulthood. Whether early life stress alone drives vulnerability to adverse adult outcomes, or whether it renders individuals more vulnerable to excessive stress levels in adulthood that, in turn, affects health and behavior, is an important question to consider. Previously we have shown that exposure to childhood trauma is highly prevalent in individuals with alcohol use disorder (AUD), and is associated with increased risk for mood and anxiety disorders. Furthermore, we have shown that emotional abuse in particular is associated with greater alcohol dependence severity, an effect mediated by neuroticism.. In the current study, we test whether current level of perceived stress mediates the associations between childhood trauma, neuroticism, and diagnoses of AUD, anxiety disorders, and mood disorders.

Methods: Subjects included 699 individuals (410 males, 289 females) screened for participation in NIAAA research protocols between 2015 and 2018: 281 individuals (198 males, 83 females) were diagnosed with moderate to severe AUD on either the Structured Clinical Interview for DSM-IV (SCID-IV) or DSM-5 (SCID-5), 113 individuals (63 males, 50 females) were diagnosed with an anxiety disorder, and 142 individuals (80 males, 62 females) were diagnosed with a mood disorder. Childhood trauma exposure was assessed with the Childhood Trauma Questionnaire (CTQ), while current stress levels were assessed with the Perceived Stress Scale (PSS). Subjects were also assessed with the NEO Personality Inventory (NEO-PIR). Path models including both direct and indirect effect estimates were evaluated using Mplus version 7. Exogenous variables included the CTQ subscales of emotional abuse, physical abuse, and sexual abuse. Outcome variables were diagnosis of AUD, any anxiety disorder (ANXD), and any mood disorder (MOOD), with neuroticism and perceived stress included as endogenous mediating variables. The path model was first fit in the total sample; multigroup analyses were then conducted to test for invariance of individual path coefficients between males and females.

Results: The path model conducted in the total sample (RMSEA = 0.06, CFI = 0.99, TLI = 0.80) revealed a significant direct effect of emotional abuse on MOOD (estimate = 0.13, $p = 0.04$, 95% CI = 0.00, 0.27), as well as indirect effects of emotional abuse on AUD (estimate = 0.13, $p < 0.0001$, 95% CI = 0.08, 0.19), ANXD (estimate = 0.19, $p < 0.0001$, 95% CI = 0.12, 0.27), and MOOD (estimate = 0.14, $p < 0.0001$, 95% CI = 0.08, 0.21), respectively, through neuroticism and perceived stress. Physical abuse had only a direct effect on AUD (estimate = 0.11, $p = 0.01$, 95% CI = 0.001, 0.22), while sexual abuse had direct effects on both ANXD (estimate = 0.13, $p = 0.001$, 95% CI = 0.02, 0.23) and MOOD (estimate = 0.11, $p = 0.03$, 95% CI = 0.005, 0.21). In multigroup analysis, two paths were found to be different in males and females: the direct path from physical abuse to MOOD, and the direct path from sexual abuse to MOOD. In males, these paths were non-significant positive associations, while in females the path from physical abuse to MOOD was a negative association (estimate = -0.329, $p = 0.01$, 95% CI = (-0.60, -0.10) and the path

from sexual abuse to MOOD was a trend-level positive association (estimate = 0.16, p = 0.08, 95% CI = -0.03, 0.33). The final model, allowing these two paths to vary between males and females while holding all other paths equal, had excellent fit (RMSEA = 0.01, CFI = 0.99, TLI = 0.99).

Conclusions: These data point to the relative roles of childhood stress/trauma and currently perceived stress levels in the development of psychiatric disorders. Exposure to emotional abuse during childhood increases vulnerability to later life stress and risk for AUD, anxiety, and mood disorders, through an increase in the personality domain of neuroticism. Alternatively, exposure to physical abuse and sexual abuse during childhood appears to have more direct effects on risk for anxiety mood disorders, with these effects differing between males and females. Future analyses will consider the influence of other potential predictors of perceived stress levels, including both environmental and genetic risk factors.

Keywords: Early Life Stress, Alcohol Use Disorder, Affective Disorders, Sex Differences

Disclosure: Nothing to disclose.

W259. Living at Altitude is an Independent Risk Factor for Increased Prescription Opioid Misuse and Fatal Overdose by Prescription Opioids

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Background: Prescription opioid misuse and fatal overdoses have increased significantly over the last two decades. Between 1999-2016, the number of fatal overdoses increased by 360%, while 4.5% of Americans misused prescription opioids in 2015-2016. Our previous studies show that living at altitude is an independent risk factor for misuse of cocaine and methamphetamine. This may be due to a hypobaric hypoxia-induced increase in dopaminergic activity in pathways implicated in addiction and reward. We thus studied the impact of living at altitude on opioid misuse and fatal overdose.

Unlike other commonly abused drugs, lethal overdose by opioids can occur through suppression of respiratory function. Opioids inhibit respiratory activity, lowering oxygen intake, and potentially leading to carbon dioxide toxicity and death. The hypobaric hypoxia inherently experienced by living at altitude is also characterized by a decrease in inspired oxygen. We therefore hypothesized that altitude-related hypoxia might exacerbate opioid-induced respiratory deficits, thereby increasing the risk for fatal overdose. In this study, we therefore examined the impact of altitude of residence on both rates of prescription opioid misuse, and fatal overdoses by prescription opioid use.

Methods: Mean state and county altitude was calculated using the Shuttle Radar Topography Mission elevation dataset.

(1) Prescription Opioid Misuse: State-level past year rates of prescription opioid misuse were retrieved from 2015-2016 National Survey of Drug Use and Health (NSDUH) conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA), which surveyed 190,106 Americans aged 12 and older. Multiple regression analyses were run to determine the relationship between state altitude and rates of misuse. State-level rates of opioid prescribing, health insurance coverage, and admissions to treatment centers for prescription opioids were included as covariates. Opioid misuse data was analyzed for the whole population and stratified by sex.

(2) Fatal Overdose by Prescription Opioids: County-level overdose data was extracted from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database. Overdose data was retrieved for the overall population and stratified by sex. Overdoses were characterized by prescription opioid overdoses of unintentional and undetermined intent between 2006-2016. Logistic regression analyses were conducted to determine the relationship between county fatal opioid overdose prevalence and county altitude, while controlling for average prescribing rates between 2006-2016 and county urbanization classification.

Results: (1) Prescription Opioid Misuse: Multiple linear regression indicated a significant positive association between mean state altitude and opioid misuse. Sex-stratified analyses however showed that this association was only present in the female population ($\beta = 0.36$, $p = 0.01$), with misuse remaining stable across altitudes for males ($p = 0.66$). Following crude analysis, models were adjusted to account for state opioid prescribing rates, rates of health insurance coverage, and state admissions to treatment centers for opioid-related problems. For females, the adjusted model accounted for 13% of the variation of state opioid misuse rates (adjusted $R2 = 0.13$, $F(5,48) = 2.4$, $p = 0.05$), with state elevation remaining significantly associated with misuse ($\beta = 0.32$, $p = 0.04$). Covariate adjustment did not impact the relationship between state altitude and rates of opioid misuse for males ($p = 0.28$).

(2) Fatal Overdose by Prescription Opioids: Odds ratios are reported for every 1,000 feet elevation gain. Logistic regression analyses indicated a significant positive association between county-level prevalence of fatal opioid overdoses and county altitude ($OR = 1.073$, $p < 0.001$). An altitude-related increase in fatal overdose prevalence was seen for both males ($OR = 1.078$, $p < 0.001$) and females ($OR = 1.102$, $p < 0.001$). Following adjustment for prescribing rates and county urbanization, the relationship between fatal overdose prevalence and altitude remained significant for both males ($OR = 1.082$, $p < 0.001$) and females ($OR = 1.062$, $p < 0.001$).

Conclusions: Epidemiological studies thus show a positive association between altitude and misuse of prescription opioids, as well as cocaine and methamphetamine. In an animal model, dopamine levels increase with altitude of housing in brain regions involved in reward and motivation, in parallel to an increase in methamphetamine preference. Hypobaric hypoxia experienced with living at altitude may thus enhance brain dopamine levels, to increase the reward benefits of drugs of abuse. These data together suggest that living at altitude may be an environmental risk factor which modulates motivation for drugs of abuse, including both stimulants and opioid painkillers.

Our study also shows an altitude-related increase in fatal overdoses by prescription opioids. In humans, maximum oxygen intake begins to decline at 2,100 feet altitude, with 46 million Americans living above this altitude threshold. Our findings suggest that doctors and policy makers in high altitude regions should consider prioritizing research on and implementation of non-opioid pain medications such as medical marijuana and mindfulness-based treatment. (Study funded by USTAR.)

Keywords: Opioid Addiction, Opioid Overdose, Environmental Risk Factors, Altitude, Hypobaric Hypoxia

Disclosure: Nothing to disclose.

W260. The Chippers, the Quitters, and the Seemingly Hooked: 12-Month Trajectories of Opioid and Cocaine Use in a Community Sample

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Background: Most scientific knowledge about opioid and cocaine use is based on studies that sample from a "tip of the iceberg" subpopulation: users in treatment. Our research clinic has been conducting a "take all comers" longitudinal study of users and nonusers, with the aim of finding natural categories of transitions among drug-career stages (e.g., nonuse to nonproblematic use, or nonproblematic use to problematic use) and predictors of those transitions.

In the analyses reported here, we examined 12-month outcomes and their predictors in participants who, at baseline, used opioids and/or cocaine, problematically or not. We assessed problems in terms of DSM-5 criteria for substance-use disorders. We were especially interested in characterizing chippers (ongoing users with few or no symptoms of addiction) and converted chippers (users whose symptoms resolve without cessation of use).

Methods: Participants were a convenience sample of Baltimore residents recruited via ads and word of mouth; none were in treatment for substance-use problems. The analyses reported here include all those who were using opioids and/or cocaine at baseline. (Nonusers were also enrolled, but their data are not reported here.) At the baseline visit (n = 290), and at a return visit 12 months later (n = 115), they completed two measures of drug use: (1) Patterns of Substance Use from the PhenX ToolKit, a semistructured interview assessing lifetime substance use and treatment; we categorized participants as current users of opioids, cocaine, or both if they reported use more than 11 times in their lifetime, and at least once in the past 30 days; (2) the DSM Questionnaire, a semistructured interview assessing 11 DSM-5 criteria for substance-use disorders during the past 30 days; we used this to categorize 12-month trajectories.

To assess environmental risk and protective factors, we characterized participants' neighborhoods of residence, using: (1) The Neighborhood Inventory for Environmental Typology (NIfETy), an onsite-observer-rated measure of physical and social disorder along specific blockfaces; (2) mean home value within a 500-meter radius of each participant's place of residence, from the Maryland Department of Assessments and Taxation.

To assess person-level risk and protective factors, we collected demographic data (sex, race, age) and used baseline scores on the Profile of Mood States (POMS), a questionnaire covering the past 30 days. In monthly phone calls, we asked about current enrollment in treatment.

To classify all ongoing drug users in terms of trajectories of DSM symptoms, we performed K-means cluster analysis on the baseline and 12-month DSM Questionnaire data (kml for single-drug users, kml3d for dual opioid/cocaine users). We then examined predictors of cluster membership, using multinomial logistic regression.

Results: For the ongoing users, the best cluster solution consisted of three groups: Symptomatic Users, with moderate or high symptom counts at baseline and month 12 (n = 46; 40%), Chippers, with few or no symptoms at either time point (n = 25; 21.5%), and Converted Chippers, with moderate or high symptom counts at baseline, but few or none at month 12, despite ongoing use (n = 25; 21.5%). We defined Quitters as a separate group, consisting of people who had not used for 30 days at month 12 (n = 19; 17%).

Multinomial logistic regression, with Symptomatic Users at the reference category, showed that the Quitters were distinct from the two clusters of ongoing users (Chippers and Converted Chippers). Quitters tended to resemble Symptomatic Users in having similarly high probabilities of dual use of opioids and cocaine, residence in disorderly or impoverished neighborhoods, nonwhite race, and mood problems on the POMS. The only ostensible protective factor that was highly likely among the Quitters (r-effect = 0.25, 95% CI 0.02-0.48) was use of opioid-agonist treatment during follow-up. In contrast, ongoing users who had few problems (Chippers) or whose problems ameliorated during the study (Converted Chippers) had high probabilities of residence in orderly neighborhoods, white race, and few mood problems on the POMS (r-effects 0.24 to 0.31, 95% CIs 0.01-0.54).

Conclusions: Among people who used opioids, cocaine, or both, the 17% who were abstinent 12 months later were similar to the 40% who were using problematically: both groups had high probabilities of what looked like risk factors for poor outcomes. The other 43%, who maintained or achieved nonproblematic use, had high probabilities of what looked like protective factors, both personally and environmentally. These findings are consistent with a "hitting bottom" model of cessation—i.e., that users who quit may be those for whom use is unsustainable. The findings are also consistent with both trait and environmental explanations for resilience to addiction among ongoing users.

One caveat is that our terminology (chippers, converted chippers, etc.) refers only to symptoms assessed at the beginning and end of a 12-month observation. Those terms are conventionally used to reflect lifetime patterns. Some of our chippers may actually have had prior histories of addiction and would therefore be conventionally called converted chippers. This does not change the overall conclusions: chippers and converted chippers are different from both quitters and ongoing symptomatic users, and the most salient difference between the latter two might be access to (or interest in) treatment.

Keywords: Cocaine Addiction, Opioid Addiction, Chipping, Longitudinal Studies, Environment

Disclosure: Nothing to disclose.

W261. Single Cell Transcriptome Profiling of Δ9-Tetrahydrocannabinol on Peripheral Immune Cells in a Healthy Individual

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Background: Cannabis is the most widely used and misused substances globally. In the U.S., cannabis use rates have doubled in the last decade. The legalization of medical and recreational use of cannabis continues to sweep across the globe. However, little is known about the molecular mechanisms of cannabis use. Previous studies have shown that Δ9-Tetrahydrocannabinol (THC), the main bioactive constituent of cannabis, has potent anti-inflammatory properties that are mediated via activating cannabinoid receptor-2 (CNR2) expressed on immune cells. THC induced expression of immune and inflammatory genes are regulated by miRNA and long non-coding RNA on immune cells. Earlier studies were conducted by using microarray or RNA-seq methods on bulk RNA samples, which lacks cell specificity and sensitivity to detect low copy transcripts. Furthermore, the specific immune cell types affected by THC are unknown. Advanced single-cell sequencing platform enables the identification of gene transcription in a specific cell. Here, we report an ex vivo study to identify gene expression by THC in specific cell types from peripheral blood mononuclear cells (PBMCs).

Methods: Two blood samples from one healthy male participant were drawn before (THC-) and 60 minutes after THC (THC +) infusion. The PBMCs from both samples were immediately isolated using Ficoll-Paque method. Single-cell RNA sequencing for 5,000 cells per sample was conducted using 10x Genomics Chromium™ Single Cell 3' Solution platform. Single cell capture, library preparation, and sequencing was performed following the recommended protocol by 10 X Genomics. Data processing and quality control was conducted by using Cell Ranger Single Cell Software. Data were normalized by applying quantile normalization in R

package. Bioinformatic analyses included: 1) cell classification: To reduce the data dimensions, we conducted principal component analysis and K-mean method for cell clustering. t-distributed stochastic neighbor embedding (t-SNE) mapping was performed on the merged gene set to identify clusters of similar cells and visualize cell clusters; 2) identification of cluster-specific genes using the differential gene expression among cell clusters, a machine-learning approach that identified signature genes for each cluster, and well established cell markers; 3) gene expression and pathway enrichment in each cell type; 4) differential cell type proportion between THC- and THC + samples; 5) cell type-based differential gene expression between THC- and THC + ; 6) cell type-based gene enrichment on differentially expressed genes.

Results: After quality control, 4,984 cells in THC- sample and 4,197 cells in THC + were successfully captured and sequenced. Mean reads per cell were 39,593 in THC- and 43,711 in THC + samples. No batch effect was observed. We classified 14 cell clusters using t-SNE mapping. The 14 clusters were merged into 9 cell types using machine learning feature selection and well-known signature cell markers. The 9 cell types were CD4 + T cell, CD8 + cytotoxic T cell, IL7 + /CD8 + T cell, B cell, Natural Killer cell, megakaryocytes, FCGR3A + Monocyte, Dendritic cell, CD14 + monocytes. Genes in the 14 cell clusters were enriched on 72 significant GO pathways including the pathways involved in the immune response and inflammation processes (i.e. regulation of cytokine production in cluster 1, pBonferroni = 0.0005). Interestingly, we found that the number of cells in 6 out of 9 cell types differed significantly between THC- and THC + samples (pBonferroni < 0.05). We identified differentially expressed genes in 7 out of 9 cell types between two samples. For example, in CD4 + T cell, transcription of IGSF1 (immunoglobulin superfamily member 1) was up-regulated in THC + relative to THC- (log2 FC = 0.20, pBonferroni = 2.40E-12). IGSF1 is thought to participate in the regulation of interactions between cells. Expression of CNR2 did not differ between THC- and THC + after Bonferroni correction. In addition, the differentially expressed genes in CD4 + cells were enriched on the transforming growth factor beta (TGFB) signaling pathway, which is involved in cellular processes in both the adult organism and the developing embryo including cell growth, cell differentiation, apoptosis, cellular homeostasis.

Conclusions: The preliminary analysis from a single healthy individual with THC administration suggests that THC shifts cell type proportions in peripheral immune cells within an hour. More impressively, THC regulates the expression of genes involving in the regulation of cell growth and cellular homeostasis. Whether the observed effects can be extrapolated to cannabis remains unstudied. Relatedly, whether other constituents of cannabis alter the effects of THC on the expression of genes involving immune and inflammatory pathways warrants further study. Nevertheless, our results show that single-cell transcriptome sequencing is a powerful approach to dissect the THC's effects in heterogeneous immune cells in PBMCs.

Keywords: Single-cell RNA Sequencing, THC, Immune Dysfunction, Pathway Analyses

Disclosure: Nothing to disclose.

W262. Low mGluR5 Availability in Emerging Adults at Risk for Addictions: Evidence of a Cannabis Use by Vulnerability Trait Interaction

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Background: The excitatory neurotransmitter glutamate has been implicated in experience-dependent neuroplasticity and drug-seeking behaviors. Type 5 metabotropic glutamate receptors (mGluR5) might play a particularly important role. In laboratory animals, mGluR5 ligands affect reward-related learning, the acquisition of drug self-administration, and the rate at which drug conditioned place preferences extinguish. In people with substance use disorders, reductions in mGluR5 availability have been observed. Since these reductions could reflect either pre-existing vulnerability traits or effects of drug use, we used positron emission tomography (PET) with the tracer [11 C]ABP688 to measure mGluR5 availability in emerging adults at elevated risk for addictions.

Methods: Fifty-nine participants (18-20 y.o.) were recruited from a longitudinal cohort that has been followed since birth (n = 2692). Based on diverse externalizing traits and behaviors (e.g., impulsivity, risk-taking and aggression) during early to mid-adolescence (11-16 y.o.) that predict future substance use problems, half of the participants were at low risk (n = 31, 20 females) while half were at high risk (n = 28, 16 females). Lifetime cannabis use histories varied markedly, and participants were divided into three groups: 1) zero (mean ± SD = 0 ± 0), 2) low (8 ± 8), and 3) high cannabis use occasions (824 ± 580). Participants were scanned on a high-resolution research tomography (HRRT) PET scanner with [11 C]ABP688 and had 3 T magnetic resonance imaging for anatomical co-registration.

Results: Compared to low risk volunteers, those at elevated risk for substance use disorders had lower [11 C]ABP688 binding values in cortico-limbic regions including the striatum (p = 0.02), amygdala (p = 0.029), insula (p = 0.041), and orbitofrontal cortex (OFC, p = 0.056). A cannabis use by risk group interaction was observed in the striatum (p = 0.025), with similar trends in the OFC (p = 0.073). In these regions, high cannabis use was associated with low [11 C]ABP688 binding in the high-risk group only. When the high risk, high cannabis use individuals (n = 9) were compared to all other participants (n = 50), [11 C]ABP688 binding values were significantly lower in the striatum (p < 0.02), OFC (p < 0.05), amygdala (p < 0.02), and insula (p < 0.05). These effects of risk group and cannabis use remained when controlling for the use of tobacco, alcohol, and all other drugs, sex and [11 C]ABP688 E-isomer percentage.

Conclusions: Emerging adults at elevated risk for addictions have lower mGluR5 availability in cortico-limbic regions. Since these reductions show an interaction with cannabis use, they plausibly reflect a drug use by risk trait interaction.

Keywords: Alcohol and Substance Use Disorders, Vulnerability Traits, Metabotropic Glutamate Receptor, Cannabis Use, Neuroplasticity

Disclosure: Nothing to disclose.

W263. Effects of Alcohol Abuse on Brain Acetate Consumption in the Living Human Brain

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Background: The liver converts ~90% of the EtOH that people drink to acetate (Ac), most of which is released to the bloodstream and oxidized for energy by other tissues. One of those tissues, the brain, normally relies primarily on glucose for energy, but it can consume significant quantities of Ac when alcohol is ingested. Binge drinkers experience frequent elevations of Ac, and because

Ac remains elevated for hours after drinking, alcohol-dependent (AD) individuals can experience prolonged periods, even several days, of high blood Ac and at higher levels than non-dependent individuals. Such repeated and prolonged exposure to Ac has the potential to affect brain metabolism. Using 13 C Magnetic Resonance Spectroscopy (MRS), we investigated the impact of chronic heavy drinking and dependence on brain Ac metabolism.

Methods: 14 alcohol-dependent subjects (AD) were admitted to the Clinical Neuroscience Research Unit for a medically supervised detoxification and one-month inpatient abstinence program. Two 13 C MRS scans were performed with [2-13 C]Ac infusions, after 4-7 days (AD1) and 21-36 days (AD2) of abstinence, respectively. A separate group of 6 AD subjects with long term sobriety (AD3) > 6 months was also recruited. For comparisons, we also recruited 15 non-dependent heavy drinkers [HD; consumed > 11 drinks/week and > 3 drinks/occasion at least once/week (for women) and > 14 drinks/week and > 3 drinks/occasion at least once/week (for men)]; and 15 light drinkers [LD; consumed < 3 drinks/week and at most 2 drinks on any given day]. During the Ac infusions, plasma Ac (total and 13C-concentrations) and brain 13C-labeled glutamate were measured in the occipital lobe. The MRS data were normalized by the plasma 13 C Ac concentration and analyzed by group with a kinetic metabolic model to assess the rate constant kac for brain Ac oxidation, where the rate of Ac consumption is given by kac*[Ac], and group uncertainties were calculated with a Monte-Carlo analysis based on the scatter of the MRS data about the kinetic fit. Statistical significances for all groups vs LD (4 comparisons) and AD1 vs AD2 and AD3 (2 comparisons) were analyzed by pairwise convolution of the probability distributions of the Ac consumption rates, using a Bonferroni correction of $4 + 2 = 6$, resulting in a cutoff for significance at $p = 0.05/6 = 0.0083$.

Results: 14 AD completed scan 1 (early detox) successfully, 11 completed scan 2 (one month), and all 6 of the separate AD3 group completed their scan. All LD and HD individuals completed their scans successfully. The rate constants kac for Ac consumption were 0.050 ± 0.003/s for LD and 0.059 ± 0.005/s for HD. For AD1, AD2, and AD3, kac was 0.025 ± 0.002/s, 0.042 ± 0.004/s, and 0.077 ± 0.005/s, respectively. Statistically, kac for HD and AD3 was significantly greater than for LD subjects ($p = 0.0056$ and < 0.0001, respectively), whereas at AD times 1 and 2, kac was less than for LD subjects ($p < 0.0001$ for both). The elevation of kac at AD2 above AD1 was not statistically significant ($p = 0.16$), but for AD3, kac was higher ($p < 0.0001$).

Conclusions: 1. The observation that brain Ac consumption is greater in HD subjects than in LD subjects confirms our previous findings and is consistent with data reported in studies using Positron Emission Tomography. The elevation in HD subjects suggests that the provision of acetate frequently and intermittently enhances further Ac consumption, potentially providing a nutritional award for times of dietary deficiencies.

2. The initial deficit of Ac consumption in the newly abstinent AD subjects suggests that the higher, more prolonged Ac elevations in actively drinking AD subjects may cause adaptive down-regulation of the capacity of brain cells to consume Ac. That deficit appears to recover with extended sobriety. In early withdrawal, if a loss of ethanol-derived Ac forms part of the withdrawal syndrome, then the reduced consumption capacity could exacerbate those symptoms. If so, Ac and possibly other monocarboxylic acids (e.g., ketone bodies) could serve as adjunct therapies for withdrawal.

3. The high Ac consumption in AD3 subjects, who have not had a drink in at least 6 months, raises the possibility of long-term effects on brain acetate metabolism induced by years of dependence, although a different group of subjects was scanned for AD3, compared to the repeated scans for AD1 and AD2.

Acknowledgements: NIAAA R01 AA021984, CTSA grant UL1TR000142.

Keywords: Alcohol Abuse, Alcohol Withdrawal, Human Brain Imaging, Metabolism, Acetate

Disclosure: Sumitomo Dainippon Pharma Co., Ltd, Consultant, UCB Pharma SA, Consultant, Yale University, Patent

W264. Preliminary MRI Evidence for Abnormalities in Neuromelanin Accumulation in the Substantia Nigra in Cocaine Use Disorder

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Background: Neuromelanin-sensitive magnetic resonance imaging (NM-MRI) is a novel method that may afford a means to interrogate the dopamine system in vivo using non-invasive MRI. Neuromelanin (NM) is a product of dopamine metabolism that accumulates slowly in neurons of the substantia nigra (SN) over the lifespan. NM-MRI has proven to be a sensitive neuroimaging marker for degeneration of dopamine neurons in Parkinson's disease. Recent work by our group has extended the applications of this technique beyond neurodegenerative conditions by validating its utility as a marker of dopamine function, thereby opening up potential applications for research in psychiatric illness. Abnormalities in the dopamine system in cocaine use disorder (CUD) have been consistently identified using PET imaging, including reduced dopamine release and D2 receptor density in the striatum and reduced VMAT-2 expression in the striatum. No studies to date have examined whether NM-MRI can capture dopaminergic abnormalities in individuals addicted to cocaine or other drugs of abuse. Here, we collected NM-MRI scans on individuals with substance use disorders (cocaine and tobacco) and healthy controls and compared the NM-MRI signal across groups.

Methods: Individuals with CUD ($n = 16$), tobacco use disorder ($n = 16$), and healthy controls ($n = 16$) were scanned using a 2D gradient-echo NM-MRI sequence with magnetization transfer on a 3 T GE MR750 scanner. NM-MRI signal was measured voxelwise within the SN relative to a midbrain white-matter reference region, thus providing an index of contrast-to-noise ratio (CNR) for each voxel within the SN. The principal analysis was a voxelwise linear regression analysis of CNR within the SN comparing cocaine users to nicotine users (nicotine users were an appropriate control group because all cocaine users also used nicotine). For significance testing we used a permutation-based method for correction for multiple comparisons and we report corrected results at $p < 0.05$. Subsequent analyses compared the other groups on NM-MRI signal extracted from the set of voxels implicated in cocaine addiction.

Results: Voxelwise analysis within the SN found cocaine users had increased NM-MRI signal compared to tobacco users (333 of 1807 SN voxels at $p < 0.05$, robust linear regression adjusting for age; $p_{corrected} = 0.020$, permutation test; peak voxel MNI coordinates [x, y, z]: -7, -25, -19 mm; mean within-mask Cohen's $d = 1.92$). The mean signal from cocaine-related voxels was also significantly higher in cocaine users than healthy controls without any substance use (one-way ANOVA with Tukey's post-hoc test, $p = 0.007$, Cohen's $d = 1.26$).

Conclusions: Our preliminary results show increases in NM-MRI signal in the SN in CUD. This evidence of increased neuromelanin concentration within the SN of cocaine users is consistent with previous reports showing cocaine-related decreases in VMAT2 expression and other studies showing a strong link between VMAT2 expression and neuromelanin formation. Future work should investigate if the signal reflects the duration or intensity of

exposure to cocaine, its specificity to cocaine use, and its relationship to addiction vulnerability. Based on these early results, NM-MRI may hold promise as a candidate non-invasive biomarker for cocaine exposure and addiction severity, one that could perhaps aid with treatment selection and response monitoring.

Keywords: Cocaine-Related Disorders, MRI, Dopamine, Neuromelanin

Disclosure: Nothing to disclose.

W265. Fronto-Striatal Tract Strength Predicts Lapse in Smokers

Abstract not included.

W266. Mu Opioid Receptor-Mediated Morphine Effects on Whole Brain Functional Connectivity Identified by Mouse fMRI

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Background: Misuse of mu opioid receptor (MOR) drugs may cause addiction and facilitate overdosing and is a leading cause to the rising opioid epidemic in North America. MORs are expressed in brain areas belonging to pain and reward pathways and, using gene knockout (KO) in mice, our laboratory demonstrated that MOR mediates both the remarkable analgesic and addictive properties of morphine (Matthes et al., 1996). MOR activation reduces aversive states such as physical or social pain and drives natural and drug reward processes (Darcq and Kieffer, 2018). Previously, we demonstrated that the MOR gene deletion in mice reshapes functional connectivity (FC) in live animals by resting-state (rs) functional magnetic resonance imaging (fMRI) (Mechling et al., 2016). Our goal is to develop a new platform to establish RsfMRI FC signatures in living mice for traditional clinically used or abused opiates, as well as for novel drugs with improved efficacy and safety profiles. In this study, we present a proof-of-principle study based of functional connectivity alterations elicited by morphine-induced MOR activation, under either isoflurane or etomidate anesthesia (Petrinovic et al., 2016).

Methods: We tested morphine effects in both wild-type (WT, on-target plus off-target effects) and MOR-KO mice (off-target effects only) in order to extract MOR-dependent effects and establish an "on-target" signature of MOR activation by the prototypic opiate drug. The approach measures morphine-induced modifications of Blood-oxygen-level-dependent signal in the brain of live WT and MOR KO animals. MRI was performed on male WT and MOR-KO mice under anesthesia, using two anesthetics: isoflurane by inhalation and etomidate by intravenous injection (Petrinovic et al., 2016). fMRI images were acquired at 7 tesla MRI scanner, equipped with a cryocoil (Bruker) with EPI sequence (TE = 17 ms; TR = 1.5 s) matrix 128×80, 15 axial slices, field of view 1.39×1.25 cm2 and 1400 volumes for total acquisition time of 35 minutes. Morphine (10 mg/kg) was injected inside the scanner after ten minutes of an initial resting state scan (Baseline). Functional data were preprocessed using a standard pipeline, and the extracted mean time series were used to perform seed-based functional connectivity (FC) analysis and Independent Component Analysis (ICA) using GIFT tools.

Results: Analyses performed with datasets from both etomidate and isoflurane anesthesia revealed similar decrease of voxelwise FC for nucleus accumbens and periaqueductal gray seeds (t-test, $p < 0.05$, cluster correction), and detailed mapping will be shown. For the ICA analysis, we extracted 20 independent components for all four groups (WT-baseline, WT-Morphine, MOR-KO-baseline & MOR-KO-Morphine) in both etomidate and isoflurane experiments, and overlapping components were identified across the two anesthetic agents. Further ICA and seed-based analyses are on-going and will be presented.

Conclusions: Our preliminary date suggest that morphine significantly modifies whole brain FC, in a manner that is dependent on its primary target (MOR) and independent from the used anesthesia procedure. Further, our data enable establishing a drug "signature", defined by whole-brain FC fingerprints using both hypothesis-free (ICA) and hypothesis-driven (seed-based) analyses. These data will also provide a reference dataset to further test other MOR opioids used in the clinic and under development, and in the future, potentially understand and predict behavioral drug effects based on the functional connectome. Finally, this platform will provide uniquely translatable information for human research and drug development.

Keywords: Opioid Addiction, Functional MRI (fMRI), Animal Research

Disclosure: Nothing to disclose.

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W267. Effect of Overnight Smoking Abstinence on a Marker for Microglial Activation: A [11 C]DAA1106 Positron Emission Tomography Study

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Background: Microglia are the main immune cells in the central nervous system and participate in neuroinflammation. When activated, microglia express increased levels of the translocator protein 18 kDa (TSPO), thereby making TSPO availability a marker for neuroinflammation. Using positron emission tomography (PET) scanning, our group recently demonstrated that smokers in the satiated state had 16.8% less binding of the radiotracer [11 C]DAA1106 (a radioligand for TSPO) in whole brain than non-smokers. We sought to determine the effect of overnight smoking abstinence on [11 C]DAA1106 binding in the brain.

Methods: Forty participants (22 smokers and 18 non-smokers) completed the two-site study and had usable data, which

included images from a dynamic [11 C]DAA1106 PET scanning session (with smokers having been abstinent for 17.9 + /1 2.3 h), a magnetic resonance imaging scan (to aid in localization of regions on the PET images), rating scales, and a blood sample for TSPO genotyping. Whole brain standardized uptake values (SUVs) were determined, and analysis of variance was performed, with group (overnight abstinent smoker vs. non-smoker), site, and TSPO genotype as factors (thereby controlling for site and genotype).

Results: Overnight-abstinent smokers had a mean 17% lower whole brain SUV than non-smokers (ANCOVA, $P = 0.0001$). The groups did not differ in injected radiotracer dose or body weight, which were used to calculate SUV. Consistent with these global findings, a significant multivariate effect of group was found (MANCOVA, $P = 0.002$) for smaller volumes of interest (VOIs), with all VOIs having a significant between-group effect on univariate analysis (range of P values < 0.0005 to 0.026), due to overnight-abstinent smokers having lower SUVs than nonsmokers (range 6.8 to 29.5%) in all VOIs studied.

Conclusions: Study results in overnight abstinent smokers are similar to those in satiated smokers, indicating that chronic cigarette smoking leads to global impairment of microglial activation which persists into early abstinence. Other explanations for study results (such as smoking leading to reduced numbers of microglia or smokers having more rapid metabolism of the radiotracer than non-smokers) are possible as well.

Keywords: Tobacco, Neuroinflammation, Positron Emission Tomography

Disclosure: Nothing to disclose.

W268. Latent Class Analysis of Youth Life Events & its Relationship to Baseline Brain Structures & 2 Year Drinking Outcomes in the NCANDA Study

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Background: Adverse life events and DSM-5 traumas experienced in youth are associated with higher rates of alcohol and substance use disorders. This study examines the relationship between baseline positive and negative life events, DSM-5 traumas, and posttraumatic stress (PTSD) symptoms; and baseline brain structures involved in cognitive control, emotional regulation, interoception, and reward processes. These measures were also examined as longitudinal predictors of adolescent and young adult alcohol use at the 2-year follow-up. This study is part of the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA), whose aims are to understand the effects of alcohol and other substances on adolescent and young adult brain development.

Methods: NCANDA is a large epidemiological multisite accelerated longitudinal, cross-sequential investigation that prospectively examines neurotrajectories of dimensions of alcohol use and binge drinking during adolescence. Baseline and yearly follow-up data were collected in adolescents and young adults (age range 12-21 years) using multimodal brain imaging, cognitive, psychological, and environmental measures to determine the neuro-markers of and the neuro-effects of alcohol and other substances on adolescent brain maturation before the onset of problematic alcohol and substance use. Baseline life event classes were modeled using a latent class analytic (LCA) approach that grouped NCANDA participants based upon their responses to the Life Events Questionnaire ($N = 474$, M baseline age = M = 14.90, $SD = 1.72$). Baseline traumatic events and PTSD symptoms were assessed using the the Computerized Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA). Brain structures were obtained using the FreeSurfer image analysis suite at baseline and yearly follow-ups. Alcohol and substance consumption were assessed with the The Customary Drinking & Drug Use Record. General linear mixed models and logistical models were used to examine baseline cross-sectional and predictive models respectively. We hypothesized that negative life events, lifetime number of traumas and PTSD symptoms would predict differences in baseline brain structures involved in cognitive control, emotional regulation, interoception, and reward processes. We hypothesized that these measures would predict moderate to heavy binge drinking at 2-year follow-up. We explored factors associated with less drinking risk at follow-up.

Results: Baseline life event classes using a latent class analyses of the Life Events Questionnaire showed an overall three-class model with interpretability that separated a 'positive' class (44.9%, $n = 213$), a 'negative' class (25.1% $n = 119$), a 'neutral' class (30.0%, $n = 142$). Covariates (sex, age, change in age, ethnicity, and socioeconomic status) were included in relation to class membership using a conservative alpha of 0.01. The positive class had the highest scores on the following five items: being a leader, acknowledgement for outstanding leadership, receiving an academic award, receiving an award outside of school, and athletic achievement. The negative class had the highest scores on the following eight items: parental work problems, parental job loss, difficult family finances, arguing with siblings, arguing with parents, arguing with parents about friends, adults in the home arguing, breaking up with a boyfriend/girlfriend. Total number of baseline type A traumas were associated with greater likelihood being in negative class ($X2 = 4.13$, $p < .05$). Latent variable class indicating neutral or typical events predicted less likelihood to transitions to moderate-heavy drinking on 2-year follow-up (odd's ratio = .46, $p < .05$) compared to the positive class). At baseline, increased gray matter in cognitive regions (parietal and temporal lobe, left frontal superior gyrus, left orbital frontal, and anterior cingulate and left subpariental thickness) were each associated with membership in the positive class ($p < .05$). The left amygdala was increased in subjects in the negative class ($p = .01$) while the right amygdala was increased in subjects in the positive class ($p < .05$) compared to the neutral class. The negative class showed larger right insula gyrus and right hippocampal volume and decreased right transverse temporal surface area and right precentral gyrus thickness than those in the neutral class ($p < .05$) indicting differences in brain regions involved in interoception, a risk factor for addiction. Having PTSD symptoms in response to trauma, but not total number of type A traumatic life events, predicted greater likelihood to transitions to moderate-heavy drinking on 2-year follow-up (odd's ratio = 4.3, $p < .05$).

Conclusions: We were able to identify a three-class model of life events, positive, neutral, and negative that were each associated with differences in brain regions involved in cognitive control and interoception. These factors are risks for alcohol and substance use disorders. The negative life event class did not measure trauma; but class membership was predicted by traumatic events indicating external validity of the three-class model. PTSD symptoms but not total trauma number predicted greater likelihood to transitions to moderate-heavy drinking on 2-year follow-up. Not having either positive or negative life events was predictive of less likelihood to transition to moderate-heavy drinking on 2-year follow-up, indicating the possibility of two pathways to problematic drinking in youth.

Keywords: Adolescence, Adolescent Alcohol, Human Neuroimaging

Disclosure: Nothing to disclose.

W269. Neurocircuitry Underlying Self-Awareness of the Need to Change Problematic Drug Use: A New fMRI Task Assessing Insight in Addiction

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Background: Individuals with addiction take drugs despite stated plans to abstain and routinely forego treatment. We have suggested that this behavior signifies more than denial, instead reflecting neurocognitive dysfunctions of insight and self-awareness. In this framework, we place special emphasis on the rostral anterior cingulate cortex (rACC) [Brodmann Areas (BA) 24, 32)] extending to the ventromedial prefrontal cortex (vmPFC) (BAs 10, 11, 25). The rACC/vmPFC, which forms part of cortical midline network that increases activation during social cognition, is thought to ascribe personal relevance or value to self-referential stimuli. Here, we developed a new fMRI task to probe the role of the rACC/vmPFC (and other cortical midline regions) in impaired insight among individuals with cocaine use disorder (CUD). We hypothesized that insight problems would be linked with aberrant self-referential circuitry.

Methods: Eighteen non-treatment-seeking individuals with CUD (per DSM-5 criteria) and a convenience sample of 15 healthy controls (to provide normative data) participated. The groups were matched on gender, race, educational attainment, and verbal IQ, but differed in age and dysphoria (CUD > control), factors covaried in the analyses. During the fMRI task, participants responded to items from the well-validated "URICA" questionnaire, which assesses motivation for behavior modification (e.g., "…I don't have any [drug use] problems that need changing"). Participants responded about the need to change their own drug use and overeating (control condition), and the need for a named friend (control condition) to change his/her drug use and overeating, which allowed crossing the factors "Substance" (drug versus food) and "Person" (self versus friend) in a 2×2 design (32 trials per condition). A Likert-style scale was used for responding (range: 1-5; strongly disagree to strongly agree; 3 = undecided). Analyses primarily tested the Substance × Person × Diagnosis 3-way interaction, with follow-up comparisons focused on the "Drug-Self" condition (i.e., participants' own drug use). To analyze the fMRI data, a region of interest (ROI) was defined in the bilateral rACC/vmPFC, using a priori coordinates from our prior studies; whole-brain analyses were also conducted. We further validated the task for use in CUD by correlating select task/neural variables with neuropsychological functioning (CANTAB battery), simulated drug-seeking behavior (choice to view drug-related versus other salient images), and addiction severity.

Results: The mean rating in CUD for the Drug-Self condition was higher than "undecided" [one-sample t-test: $p = 0.001$], but lower than "agree" [one-sample t-test: $p = 0.036$], consistent with a mild insight impairment. When including controls into a full ANCOVA (covariates: age and dysphoria), CUD reported a greater need for behavior change than controls across all task conditions (Diagnosis main effect: $p = 0.001$). Although the 3-way interaction was not significant, the Drug-Self condition differed between the groups as expected (CUD > control; $p < 0.001$). In ROI analyses of the bilateral rACC/vmPFC, the 3-way interaction was significant ($p < 0.001$), such that activation was lower in CUD than controls uniquely during the Drug-Self condition ($p = 0.024$) (all other conditions: $p > 0.12$). Whole-brain interactions emerged in the occipital cortex, dorsal ACC (dACC), and dorsomedial PFC (dmPFC) (all $p < 0.05$, cluster-corrected) (though the dACC and dmPFC were attenuated after correction for covariates). Within CUD, a lower self-reported need to change one's drug use was correlated with greater simulated drug-choice and worse free recall memory; lower rACC/vmPFC activation was correlated with greater severity of dependence and worse free recall memory (all $p \leq 0.01$). Importantly, task behavior and rACC/vmPFC activation were negatively correlated across all participants ($p = 0.003$).

Conclusions: Individuals with CUD reported a greater need to change their behavior (including drug use) than controls (who had no drug use problems). Yet, despite impairment severe enough to warrant DSM-5 diagnosis, CUD individuals did not "agree" they needed to alter their drug use. As hypothesized, self-judgments of the need to curb drug use were linked with activation in the rACC/vmPFC (and other cortical midline regions, such as the dACC and dmPFC) while participants made the judgments. These activations were lower in CUD than controls, suggesting that self-referential processing (e.g., self-awareness of addiction severity) is altered in addiction, which may help sustain the addictive behavior. Indeed, lower self-reported need for behavior change and lower rACC/vmPFC activations correlated with worse functioning in CUD. Our results support prior work (from our lab and others) that has linked rACC/vmPFC function and structure to behavioral markers of insight and self-awareness, such as self-monitoring of task performance. However, by simultaneously measuring behavioral and neural markers of insight, our study advances these prior studies, which have assessed constructs less directly related to insight or have examined neuroimaging associations with insight measures collected outside the scanner. Insight and its underlying circuitry may provide a novel therapeutic target in addiction, potentially relevant to decreasing unreflective, compulsive drug use while increasing motivation to seek help.

Keywords: Self-Referential, fMRI, Drug Addiction, Insight, Anterior Cingulate Cortex

Disclosure: Nothing to disclose.

W270. Association of Dopamine D1-Type Receptors in Prefrontal Cortex With Cognitive Impulsivity: Impact of Methamphetamine Use

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Background: Impulsivity is a multifaceted personal trait, characterized by deficits in self-control that are manifested as impetuous behaviors with lack of deliberate thinking. Individuals with stimulant-drug dependence exhibit impulsivity, which is considered to be a factor in vulnerability to drug use disorders. Ample evidence suggests the involvement of dopaminergic signaling and frontostriatal circuits involved in 'top-down' control. Dopamine D1-type receptor availability measured as binding potential (BPND) in the dorsolateral prefrontal cortex (DLPFC) of patients with schizophrenia-spectrum disorders is higher than in controls and negatively associated with working memory performance. Working memory has been shown to have a moderating effect on impulsiveness in addictive populations, and a recent meta-analysis indicates that DLPFC function underlies working memory and self-control. Nevertheless, little has been reported on D1-type receptor in individuals with methamphetamine (MA) dependence and its potential relationship with impulsivity.

Methods: Positron emission tomography (PET) was utilized to measure D1-type BPND in DLPFC in 18 healthy-control subjects and 19 with MA dependence. Working memory was measured by Trail-making test (TMT) A and B, and Spatial Sternberg task. Self-reported impulsivity was measured using Barratt Impulsiveness Scale-11 (BIS-11), and a recently-verified two factor model was employed to calculate scores of cognitive and behavioral impulsivity.

Results: D1-type BPND in DLPFC was higher in MA group than control group (F1, 32 = 7.807, p = 0.009). In controls, but not in MA group, BPND was positively correlated with BIS-Cognition (Control: r = 0.689, p = 0.005; MA: r = 0.061, p = 0.821) and negatively correlated with working memory measured with TMT (Control: r = 0.593, p = 0.02; MA: r = 0.297, p = 0.28)and Spatial Sternberg Task (Control: r = -0.657, p = 0.011; MA: r = -0.354, p = 0.26).

Conclusions: These results do not only replicate relationship of D1-type BPND in DLPFC with working-memory performance but also suggest an important role of dopaminergic signaling through DLPFC D1-type receptors in impulsivity and other mechanism(s) contributing greater impulsivity in MA dependence.

Keywords: D1 Dopamine Receptors, Dorsolateral Prefrontal Cortex, Methamphetamine, Positron Emission Tomography

Disclosure: Nothing to disclose.

W271. Intravenous Administration of Ghrelin Increases Blood Cortisol and Aldosterone Concentrations in Heavy-Drinking Alcohol-Dependent Individuals: Results From a Double-Blind Placebo-Controlled Human Laboratory Study

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Background: Increasing evidence supports the role of appetite-regulating pathways, including ghrelin, in alcohol use disorder (AUD). This study tested the hypothesis that intravenous (IV) exogenous ghrelin administration increase endogenous serum cortisol and aldosterone levels, and that changes are predictor of alcohol craving.

Methods: This was a double-blind, placebo-controlled human laboratory study in non-treatment-seeking, alcohol-dependent, heavy-drinkers (n = 45) randomized to receive either 0 mcg/kg (placebo), 1 mcg/kg or 3 mcg/kg IV ghrelin. Participants, then underwent a neutral (juice) and alcohol cue-reactivity procedure.

Results: There was a main effect for dose IV ghrelin administration in increasing both endogenous serum cortisol and aldosterone levels (p's < 0.0001). For cortisol, there was also a main effect for time and for dose IV ghrelin by time interaction (p's < 0.0001). The increase of serum cortisol level predicted the increase of urge to drink alcohol (p < 0.05) but not urge to drink juice (p = n.s.) in dose dependent manner, as reflected by the main effect of dose IV ghrelin and by the cortisol by dose IV ghrelin interaction (p's < 0.05). The increase of serum aldosterone level, however was not a predictor of either increase of urge to drink alcohol or juice (p = n.s.).

Conclusions: These findings provide preliminary evidence of ghrelin effect on the glucocorticoids and mineralocorticoids pathways in individuals with AUD and suggest that their relationship may play a role in alcohol craving.

Keywords: Alcohol Use Disorder, Ghrelin, Cortisol, Aldosterone

Disclosure: Nothing to disclose.

W272. End-Of-Day Reports of Daily Hassles and Stress in Men and Women With Opioid-Use Disorder: Relationship to Momentary Reports of Drug Use and Stress

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Background: Stress can be validly assessed "live" or in a summary, evaluative way in the very recent past. We assessed both ways in a sample of opioid- and cocaine-using men and women, using smartphone-based ecological momentary assessment (EMA) combined with end-of-day (EOD) entries. Our objectives were: (1) to characterize the hassles experienced by outpatient opioid and cocaine users and how these varied by sex, and (2) to assess how whole-day EOD reports of hassles, as well as EOD reports of current mood and perceived stress, were associated with live reports of drug use and stress events from the same days, and how these associations differed by sex.

Methods: The participants in this study were enrolled in a large 46-week natural-history study of stress, geographical location, and drug use. For up to 16 weeks, 161 outpatients with opioid-use disorder in opioid-agonist treatment carried smartphones on which they reported stressful events (SEs) and drug use (DU) and completed an EOD questionnaire to report hassles they encountered throughout the day, current perceived stress, current mood, and number of cigarettes smoked. We compared EOD responses on days with and without SE and DU reports and on days when thrice-weekly urine drug screens indicated opioid use, cocaine use, or abstinence.

Results: Participants (N = 161) made 11,544 EOD entries; EMA stressful events were reported on 861 (7.5%) days, and drug use on 1685 (14.6%) days. The most frequently reported hassles in EOD entries were "not enough money" (31.4% of daily reports) and maintaining abstinence (18.7%). Total EOD hassles showed small but statistically significant associations [odds ratios (95% CIs)] with EMA reports of stressful events [1.09 (1.06-1.13)], drug uses [1.08 (1.06-1.10)], and urine-positive opioid [1.06 (1.04-1.09)] and cocaine [1.03 (1.00-1.06)] results. Men (N = 117) and women (N = 44) had similar rates of hassles (mean/day ± SD): men 2.25 ± 3.55; women 2.55 ± 3.76 (F1,159 = 0.53, p = 0.47). Smoking at least 10 cigarettes per day was associated with opioid use and with drug events (but not stress events).

Conclusions: The end of day assessment of hassles was a useful addition to ecological momentary assessment. Hassles pertaining to not having enough money and substance use were prevalent and differentially associated with stressful events and drug use. Men and women reported similar rates of daily hassles. Monitoring hassles and devising specific coping strategies might be useful therapeutic targets.

Keywords: Ecological Momentary Assessment, Perceived Stress, Drug Use, Sex Differences

Disclosure: Nothing to disclose.

W273. Chronic Dopamine Detection With a 16-Channel Carbon Fiber Microelectrode Array

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Background: One goal for understanding neuroplasticity is to chronically record both neurotransmitter activity and electrical

activity from the brain of freely moving animals. Carbon fiber electrodes are well suited to address the challenges of chronic recording as they can be used for both fast-scan cyclic voltammetry (FSCV) to measure dopamine (DA) and electrophysiology. Chronic multichannel electrodes were constructed to look at changes in DA release and electrophysiology associated with long-term adaptation of behaviors, such as the development of addiction. FSCV is a technique of choice for questions that involve in vivo DA signaling due to its sub-second temporal resolution and high sensitivity. Distinct populations of DA neurons projects to sub-regions within the nucleus accumbens (NAc). Medium spiny neurons of the NAc core and shell are thought to mediate unique aspects of behaviors coded by the DA signal. One goal for these electrodes is to determine the dynamics of DA signaling simultaneously from these two regions as they relate to ongoing behaviors.

Methods: 16-channel carbon fiber arrays, constructed in-house as part of the Brain Initiative, were implanted in rats aimed at the nucleus accumbens. Electrophysiological and DA recordings were obtained from male and female rats over a 60-day period of time. Tissue was obtained after 60 days post-implantation and sectioned with the electrodes in place to determine tip location and viability of neurons close to the electrodes.

Results: With this novel tool, changes in DA release and induced by electrical stimulation of the ventral tegmental area (VTA) and spontaneous electrophysiological recordings were obtained in nucleus accumbens core and shell for over 60 days, for the first time. We saw dopaminergic activity when the VTA was stimulated. This stimulation serves as a positive control and confirms that the arrays were implanted in the correct region. Furthermore, we found that exposure to a conspecific of the other sex induced DA release, and chronic oxytocin treatment modulated VTA-induced DA release selectively in NAc shell and NAc core. Within a tissue section, carbon fibers were easily identified in the bright field images and followed along the length of the exposed fiber area. The neuron density within the first 100 µm, where the electrodes was not significantly different from neuron densities at 175-200 µm.

Conclusions: The 16-channel carbon fiber array represents, to our knowledge, the first "tri-functional" electrode array, capable of 1) chronic electrophysiology, 2) chronic chemical sensing, and 3) precise identification of recording locations. The ability to relate DA signals to surrounding macro- and micro-structure will be highly valuable for understanding both natural signals related to learning and motivation and the altered signaling produced by drugs of abuse related to addiction-like behavior.

Keywords: Dopamine, Nucleus Accumbens, Fast Scan Cyclic Voltammetry

Disclosure: Nothing to disclose.

W274. Circadian- And Sex-Dependent Increases in Intravenous Cocaine Self-Administration in NPAS2 Mutant Mice

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Background: The development of substance dependence is associated with disruptions in circadian rhythms and circadian genes. In mice, a dominant negative mutation in circadian locomotor output kaput (CLOCK) increases both cocaine reward and self-administration. Interestingly, our previous studies found that a mutation in its suggested paralogue, neuronal PAS domain protein 2 (NPAS2), show a decrease in cocaine reward. However, the role of NPAS2 in cocaine self-administration remains unknown.

Methods: Here we performed intravenous cocaine self-administration using male and female mice with a mutation in Npas2 during the light or dark phase. Mice first acquired an operant response for food and then were implanted with an indwelling jugular catheter. After recovery, mice acquired cocaine self-administration and then dose-response testing was conducted, both at a fixed ratio and progressive ratio schedule.

Results: While the Npas2 mutation did not impact acquisition of a food-reinforced response, it surprisingly enhanced acquisition of a cocaine-reinforced response, particularly in females. More specifically, Npas2 mutant mice took more infusions of cocaine and acquired the response faster. The reinforcing properties of cocaine were also increased in mutant mice, whereas motivation was only moderately increased in females. Interestingly, these sex differences became greater during the dark phase with Npas2 mutation increasing cocaine intake, as well as the reinforcing and motivational properties of cocaine, extinction responding, and cue-induced reinstatement.

Conclusions: These results suggest that NPAS2 affects reward in a circadian-dependent manner. Importantly, females appear to be more impacted by the Npas2 mutation, particularly during the dark phase. Further research is required to understand why and how NPAS2 regulates cocaine intake across phase and in a sex-dependent manner.

Keywords: Drug Addiction, Circadian Rhythm, Self-Administration, Sex Differences

Disclosure: Nothing to disclose.

W275. Effects of Lorcaserin on Drug Word-Elicited Cortico-Hippocampal Connectivity in Opiate Use Disorder

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Background: The selective 5-HT2CR agonist lorcaserin reduces drug self-administration in preclinical studies and has shown initial efficacy in smoking cessation. To determine whether lorcaserin affects neurocircuits pertinent to opiate motivation and memory in humans, we examined the effects of subchronic lorcaserin administration on drug-related cue reactivity in individuals diagnosed with opioid use disorder (OUD) or both opiate and cocaine use disorder (OCUD).

Methods: Participants met DSM-5 criteria for OUD based upon use of a single or multiple opioid substances. Eleven OUD and 13 OCUD participants underwent fMRI while performing an opioid-word Stroop task at baseline (Day 1) and one week later (Day 8). During the task, opioid words (OW) and neutral words (NW were presented to participants, who were instructed to indicate the color of each word with a button press. Prior to the baseline scan, all participants received placebo (PLC). Following the baseline scan, OUD ($n = 6$) and OCUD ($n = 6$) participants received 10 mg of lorcaserin daily for one week. Placebo was administered to the other participants (OUD $n = 7$; OCUD $n = 5$). Dynamic causal modeling (DCM) was used to measure effective (directional) connectivity (EC) between salience network and other nodes consistently recruited by drug cues during fMRI. Based on previous studies, we focused on EC from left (L) anterior cingulate cortex (L ACC) to right hippocampus (R HIPP) and R medial orbitofrontal cortex (MOFC) to R HIPP. DCM analysis was conducted to measure the within-participants differential change of EC (Day 8 minus Day 1) in lorcaserin-vs. PLC treatment. Each EC is expressed the modulatory effect of OW over the NW (EC during OW trials minus EC during NW trials).

Results: Relative to PLC, lorcaserin increased L ACC to R HIPP EC for both OUD participants (from 0.0106 Hz to 0.0780 Hz) and OCUD participants (from 0.0230 Hz to 0.0656 Hz). lorcaserin decreased R MOFC to R HIPP EC (from 0.1248 Hz to 0.0160 Hz) in the OUD participants but did not significantly alter that connectivity in OCUD participants.

Conclusions: Lorcaserin increased communication from cognitive control nodes to episodic memory-related nodes when OUD and OCUD participants were confronted with opiate-related stimuli. Simultaneously, lorcaserin decreased connectivity from reward-valuation nodes to episodic memory-related nodes in OUD, but not OCUD. These data suggest that lorcaserin alters connectivity with episodic memory circuits in persons with OUD when they are confronted with opiate-related stimuli.

Keywords: Opiate Addiction, Serotonin 5-HT2C Receptor, Functional MRI (fMRI), Task-Based Functional Connectivity

Disclosure: Nothing to disclose.

W276. A Deeper Insight Into How GABA-B Receptor Agonism via Baclofen May Affect Alcohol Seeking and Consumption: Lessons Learned From a Human Laboratory Investigation

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Background: Previous studies suggest that GABA-B receptor agonism may represent an effective pharmacological intervention for treating addictive disorders. Baclofen is a selective GABA-B receptor agonist which has been investigated as a potential treatment for alcohol use disorder. In animal models, baclofen administration reduces alcohol intake and suppresses acquisition, maintenance and reinstatement of alcohol seeking behavior. Despite these promising findings from preclinical experiments, human studies with baclofen have demonstrated mixed results. While treatment with baclofen has been shown to reduce alcohol craving and drinking and to prolong abstinence in some randomized controlled trials, other studies have found baclofen not being superior to placebo in affecting alcohol-related outcomes. Additional research is required to understand the biobehavioral mechanisms underlying baclofen's effect on alcohol use. Well-controlled human laboratory studies provide an informative platform to address this question.

Methods: In the present randomized, double-blind, placebo-controlled study, thirty-four male and female alcohol-dependent individuals were randomized to receive baclofen or placebo for one week. The initial dose of baclofen was 15 mg/day (5 mg t.i.d.; titration phase) for 3 days, followed by 30 mg/day (10 mg t.i.d.; target dose). After being on the target dose for at least 4 days, participants underwent an alcohol laboratory experiment. The experimental session included three consecutive procedures: (1) alcohol cue-reactivity (water trial followed by two alcohol trials), (2) fixed-dose alcohol priming (40 minutes, target blood alcohol concentration: 0.03 g/dL), (3) alcohol self-administration (2 h, up to 8 mini-drinks). During the laboratory experiment, craving and other subjective responses to alcohol were assessed, and blood samples were collected for pharmacokinetic measurements. The effects of baclofen on the relationships between different alcohol-related laboratory parameters were investigated. A liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay was developed to quantify baclofen in the plasma samples obtained during this study. Baclofen pharmacokinetic parameters and their associations with behavioral measures were also examined.

Results: Baclofen disrupted the link between alcohol priming and self-administration, as indicated by significant interaction effects between drug condition (baclofen versus placebo) and priming variables [alcohol craving: $F(3,9) = 6.03$, $p = 0.01$; alcohol sedation: $F(3,6) = 7.16$, $p = 0.01$; breath alcohol concentration: $F(1,25) = 5.22$, $p = 0.03$] on the total amount of alcohol self-administered. A similar pattern was observed for other alcohol-related subjective responses, but the interaction terms did not reach statistical significance. Baclofen did not affect the relationship between cue-induced alcohol craving during cue-reactivity and the amount of alcohol self-administered during alcohol self-administration. Considerable inter-individual variability in baclofen pharmacokinetics was observed. Baclofen pharmacokinetic parameters were calculated as follows (mean ± standard error): maximum plasma concentration (Cmax) = 84.90 ± 13.58 ng/mL; time to Cmax (tmax) = 2.47 ± 0.21 h; apparent plasma clearance at steady state (CLss/F) = 60866.52 ± 12641.72 mL/h; half-life (t1/2) = 4.42 ± 0.29 h; area under plasma concentration - time curve (AUC) = 1033.49 ± 97.77 h*ng/mL. Bivariate correlation analyses between pharmacokinetic parameters and behavioral outcomes showed that baclofen Cmax negatively correlated with cue-induced alcohol craving ($r = -0.57$, $p = 0.03$) and priming-induced ratings of 'like more' ($r = -0.59$, $p = 0.02$).

Conclusions: In the present study, baclofen administration led to a dissociation of the link between an initial drink (priming) and subsequent alcohol consumption (self-administration). This observation is consistent with preclinical experiments in which baclofen has been shown to block priming-induced reinstatement and escalation of drug use. GABA-B receptor agonism, in combination with alcohol, may pose an additive or synergistic effect on GABAergic neurons and decrease the amount of alcohol needed to have the same effect on GABAergic neurotransmission. While electrophysiological studies are required to test this hypothesis, our behavioral findings show that GABA-B receptor agonism via baclofen modulates the response to an initial drink, such that subsequent drinking is less reinforced. The pharmacokinetic-behavior analyses provided a deeper insight into baclofen's effects on alcohol-related outcomes. For example, while baclofen was not superior to placebo in reducing cue-induced alcohol craving in our aggregate analyses, higher blood concentrations of baclofen were associated with lower craving for alcohol during the cue-reactivity. Considerable pharmacokinetic variability is an important factor to take into account when studying/using baclofen as a treatment for alcohol use disorder.

Keywords: GABA-B receptors, Baclofen, Alcohol, Craving, Subjective Response

Disclosure: Nothing to disclose.

W277. Medial Prefrontal Cortex Kappa Opioid Receptors and Alcohol Dependence-Induced Working Memory Deficits

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Background: A fundamental characteristic of alcohol use disorders is the loss of control over alcohol consumption that facilitates the progression to alcohol-dependence. Given the comorbidity of alcohol dependence and disorders of affect such as depression is extremely high, it has been posited that self-medication of negative affective states contributes to continued excessive alcohol use and relapse. Furthermore, negative affective states produced by chronic alcohol exposure can influence the neurocircuitry of cognitive control systems to perpetuate further excessive alcohol use. Once that degree of dysregulation is reached, components of the dependence cycle serve to facilitate

each other in a manner that is extremely deleterious. Impaired working memory is one symptom contributing to compromised executive function in alcoholics. Dysregulation of cortical dynorphin (DYN) and κ-opioid receptors (KORs) has been implicated in alcoholism-induced impairment in executive function.

Methods: The present experiments test the hypothesis that medial prefrontal cortex (mPFC) KORs contribute to impaired working memory in alcohol dependence. Alcohol dependence was induced in male Wistar rats via chronic intermittent alcohol vapor exposure prior to training / testing in an mPFC-dependent working memory task (delayed nonmatching-to-sample task; DNMST) during acute withdrawal with somatic withdrawal signs and escalated alcohol self-administration measured to confirm the presence of a dependence-like state. By comparing mPFC KOR function in young and mature alcohol-naïve rats to that of mature alcohol-dependent rats using a DYN A-stimulated [35 S]GTPγS coupling assay, alcohol dependence-induced mPFC KOR dysfunction could be identified. Importantly, a functional role for mPFC KORs in the regulation of working memory deficits in alcohol dependence was assessed through intra-mPFC infusions of a KOR agonists and antagonists prior to assessment in the DNMST.

Results: In alcohol-dependent rats displaying somatic signs of withdrawal, impaired DNMST performance confirmed compromised working memory that was paralleled by intra-mPFC KOR activation in alcohol-naïve animals. Furthermore, DYN A-stimulated mPFC KOR function declined to negligible levels with age but was pathologically rekindled in older alcohol dependent rats. Importantly, mPFC KOR involvement in alcohol dependence-induced working memory deficits was functionally confirmed by intra-mPFC KOR antagonism that ameliorated impairments in working memory during acute withdrawal.

Conclusions: Regulation of working memory by mPFC KORs and alcohol dependence-induced dysregulation of mPFC KOR function identify a novel therapeutic target to treat neuropsychiatric disorders defined by symptoms of working memory impairment.

Keywords: Kappa Opioid Receptor, Alcohol Dependence, Working Memory, Medial Prefrontal Cortex, Age Effects

Disclosure: Nothing to disclose.

W278. Biased Signaling of the Mu Opioid Receptor Revealed in Neurons

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Background: Over-production and prescription of opioids, has evolved into a major opioid crisis impacting North America. Biased agonists for Mu Opioid Receptors (MORs) are emerging drugs that are proposed to produce the desired Gi/o-effect of pain relief without unwanted βarrestin2-effects such as euphoria or respiratory depression. The concept of biased signaling raises the possibility of developing drugs with improved efficacy and safety profiles, yet translation of this concept to native tissues remains a major challenge.

Methods: Here, we selected preclinical (Met-Enkephalin, DAMGO, Endomorphin-1), clinical (Fentanyl, Loperamide, Oxycodone, Morphine, Buprenorphine) and novel biased MOR agonists (TRV130, PZM21) to profile their activities in two experimental systems. First, to parallel drug screening at pharmaceutical companies, we employed transfected MORs in HEK-293 cells and used resonance energy transfer (RET) biosensors. Second, to examine endogenous MOR activities, we generated and fully characterized new knock-in mice expressing physiological levels of functional and fluorescent MORs to generate examine drug activities at native MORs in neurons using confocal microscopy. Males were used for the pharmacological screening in knock-in mice.

Results: In both systems, three subgroups of drugs emerged (i) high Gi/o and βarrestin2 signaling, (ii) low Gi/o and βarrestin2 signaling and (iii) Gi/o biased signaling. When MOR trafficking was evaluated using two assays, agonist induced MOR redistribution to intracellular compartments and MOR translocation into early endosomes, the drug activities at transfected or endogenous MORs were strikingly similar.

Conclusions: Our data show closely correlated drug activities in these otherwise highly distinct experimental systems. Our study reveals strongest Gi/o-bias for buprenorphine, which should be promoted in the clinic for pain patients and demonstrates the physiological reality of biased signaling for mu opioid drugs.

Keywords: Drug Discovery, Knock-in Mouse, GPCR, RET Biosensors

Disclosure: Nothing to disclose.

W279. The Role of the Interleukin-1 (IL-1) System in Alcohol Dependence-Induced Cortical Dysfunction

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Background: Neuroimmune pathways regulate brain function to influence complex behavior, and their dysfunction is associated with several neuropsychiatric diseases, including alcohol use disorders. In particular, the interleukin-1 (IL-1) system has emerged as a key regulator of the brain's response to alcohol. IL-1β expression is elevated in the brains of human alcoholics and ethanol-dependent rodents, and exogenous IL-1β treatment in rodents regulates inhibitory transmission in key addiction-related brain regions, promotes alcohol-induced neuroinflammation and potentiates withdrawal-induced anxiety. Moreover, the IL-1β neuroinflammatory response of ethanol-dependent rodents is associated with significant cognitive deficits. Therefore, here we investigated the mechanisms underlying alcohol-induced neuroadaptation of IL-1 signaling at GABAergic synapses in the prelimbic region of the medial prefrontal cortex, an area responsible for drug-seeking behaviors.

Methods: We induced ethanol dependence by exposing C57BL/6 J male mice to the chronic intermittent ethanol vapor-2 bottle choice paradigm (CIE-2BC) and used whole-cell voltage clamp electrophysiology to record spontaneous inhibitory postsynaptic currents (sIPSCs) in prelimbic cortex layer II/III pyramidal neurons. sIPSC frequency, amplitude and kinetics were analyzed using Mini Analysis (Synaptosoft Inc., Fort Lee, NJ) and all final values were analyzed for independent significance using one-sample t-tests and compared using t-tests or one-way ANOVA with Bonferroni post hoc analyses with Prism 5.02 (GraphPad, San Diego, CA). Data are presented as mean ± standard error of the mean (SEM), with a minimum of 6 cells from 4 animals used for each experimental condition.

Results: We found that IL-1β (50 ng/mL) significantly reduced inhibitory input onto prelimbic cortex layer II/III pyramidal neurons in naïve mice ($p < 0.01$) but enhanced it in ethanol-dependent mice ($p < 0.01$). To uncover potential neuroadaptive mechanisms, we next examined whether these effects are sensitive to acute ethanol. In naïve mice, ethanol (44 mM) alone had no effect on

GABA transmission, but IL-1β in the presence of acute ethanol increased GABA release (similar to the effects of IL-1β alone in dependent mice; $p < 0.01$). Importantly, a 15 min washout of acute ethanol restored the ability of IL-1β to decrease GABA release in naïve mice. These interactions between the IL-1 system and acute and chronic ethanol involve both pro-survival (PI3K/Akt) and pro-inflammatory (MyD88/p38) intracellular cascades; Akt (200 nM MK-2206) or PI3K inhibition (50 μM LY294002) produced an IL-1β-induced increase in GABA release in naïve mice (both $p < 0.01$), while in dependent animals IL-1β's potentiation of GABA release was blocked by a p38 MAPK inhibitor (20 μM SB202190) or a MyD88 mimetic (AS-1, 50 μM) that prevented MyD88 recruitment to the IL-1 receptor complex. Potential chronic ethanol-induced changes in the expression of IL-1 signaling molecules and these two intracellular cascades are currently being assessed using several molecular biology methods.

Conclusions: Collectively, our results indicate that IL-1 signaling can induce pro-survival or pro-inflammatory responses in the medial prefrontal cortex, and that alcohol dependence produces a sustained pro-inflammatory bias to increase cortical inhibition. As the IL-1 receptor antagonist (kineret) is FDA approved, this work underscores its potential for treating the hypofrontality associated with alcohol use disorders.

Keywords: Neuroimmune Mechanisms, Alcohol Dependence, Medial Prefrontal Cortex, Interleukin-1, GABA Transmission

Disclosure: Nothing to disclose.

W280. Sex-Related Hormone Levels Associations With Alcohol Dependence and Alcohol Craving

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Background: Clinical and epidemiological studies indicate that both gender and sex-related differences influence susceptibility, progression and treatment response in alcohol-dependent subjects. Moreover, reports indicate that sex and gender-specific differences impact alcohol craving and alcohol consumption in positive and negative emotional states by alcohol dependent subjects and non-dependent alcohol users. Although biological mechanisms underlying these differences remain poorly understood, it is reasonable to assume that sex-related hormones play an important role in the above-mentioned differences. In this study, we aimed to investigate the associations of the sex-related hormone's/protein's levels with alcohol dependence and alcohol craving in male and female subjects.

Methods: Levels of sex-related hormones (estradiol, estrone, total testosterone, progesterone, follicle stimulated hormone [FSH], luteinizing hormone [LH]), and sex hormone binding globulin [SHBG] were measured by mass spectrometry methods or automated immunoassays in plasma samples from 44 subjects (29 males and 15 females; mean age = 45.9+/-15.6) meeting DSM-IV-TR criteria for alcohol dependence (AD) and 44 age-, sex- and race-matched non-alcohol dependent controls. Penn Alcohol Craving Scale (PACS) was used to assess alcohol craving intensity. Inventory of Drug Taking Situations (IDTS) was used to assess propensity to drink in positive or negative emotional situations or due to strong temptation to drink. Conditional logistic regression analyses were conducted to examine the association of the tested sex-related hormone's/protein's levels with the risk for alcohol dependence and alcohol craving scales, accounting for matching variables.

Results: FSH level was significantly higher in alcohol dependent males compared to controls (AD vs controls: 10.3+/-9.8 IU/L vs 8.0 +/-15.9 IU/L; $P = 0.005$, Pcorrected = 0.035). We further observed a significant inverse negative correlation between FSH level and propensity to drink in negative emotional situations (Spearman's rho = -.540; $P = 0.021$), as well as a positive correlation between progesterone level and craving intensity (Spearman's rho = .464; $P = 0.020$) in male AD subjects.

Conclusions: This pilot study revealed several important findings. Firstly, consistent with previous reports, we identified a significantly higher plasma FSH level and a relatively trend for increased higher SHBG level in AD males compared to control males. Secondly, we discovered a significant negative correlation between plasma FSH level and propensity to drink in negative emotional states (measured by IDTS negative subscale) along with a significant positive correlation between plasma progesterone level and the intensity of craving (measured by PACS score) in AD males. These findings support the hypothesis that sex-related hormones are associated with sex differences in the risk for alcohol dependence as well as craving-related phenotypes. However, it remains unclear if this involvement is temporary in nature (i.e., state or trait-dependent), causative (i.e., alcohol use triggers the change of sex-related hormone levels or vice versa), or the combination of both. Future research is needed to replicate these findings and investigate the biological mechanisms underlying these associations.

Keywords: Alcohol Dependence, Sex Hormones, Craving, Sex Differences

Disclosure: Nothing to disclose.

W281. Sex-Dependent Effects of Amphetamine in Adolescence on Dopamine and Cognitive Development: Role of the DCC Pathway

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Background: Initiation of drug use in adolescence is associated with an enduring increase risk of progressing from recreational use to addiction. This peak age for drug initiation coincides with a critical period in mesocorticolimbic dopamine development, which is orchestrated by the Netrin-1 guidance cue receptor DCC. Briefly, DCC receptors promote target recognition events of dopamine axons in the nucleus accumbens in adolescence, preventing them from continuing to grow to the prefrontal cortex. Our previous work shows that, in male mice, exposure to amphetamine in adolescence downregulates Dcc expression in dopamine neurons. This, in turn, disrupts the ongoing establishment of mesocorticolimbic dopamine connectivity, leading to deficits in reward and cognitive performance in adulthood. Whether exposure to the same amphetamine regimen in adolescence induces similar changes in female mice remains unknown.

Methods: We treated male and female C57BL6 mice with an intraperitoneal regimen of amphetamine (4 mg/kg, producing peak plasma levels similar to human recreational use) or saline during early adolescence (postnatal day 22 ± 1 to 31 ± 1). Using quantitative analysis of gene and protein expression, neuronal connectivity, and behavior, we then examined (a) Dcc mRNA expression in the ventral tegmental area one week after treatment, (b) Netrin-1 protein expression in the nucleus accumbens one week after treatment, (c) dopamine connectivity in the nucleus accumbens and medial prefrontal cortex in adulthood, (d) performance on behavioral inhibition, motivation, and risk-taking-like behavior tasks in adulthood.

Results: In contrast to our previous findings in males, amphetamine does not alter Dcc expression in dopamine neurons in female mice one week after treatment, indicating that amphetamine exposure regulates Dcc expression in dopamine neurons not only in an age-dependent (Yetnikoff et al; 2007, 2011, 2013), but also in a sex-specific manner. Furthermore, amphetamine in adolescence downregulates Netrin-1 levels in the nucleus accumbens of male, but not female mice. When compared to their saline-treated littermates, adult males that were exposed to amphetamine in early adolescence showed impaired behavioral inhibition, increased risk taking-like behavior, and an inability to adapt to changing reward contingencies. However, these drug-induced behavioral alterations were not observed in female mice. We are currently assessing the effects of the amphetamine or saline regimens on dopamine connectivity in adult female mice.

Conclusions: In males, amphetamine exposure in early adolescence disrupts the development of mesocortical dopamine connectivity in a Netrin1/DCC-dependent manner, leading to cognitive alterations in adulthood that are associated with addiction vulnerability. Strikingly, exposure to the exact same amphetamine regimen does not lead to these molecular and behavioral changes in female mice. Research in humans show important differences in incidence of psychiatric conditions, including substance abuse, between women and men. Our preclinical research investigating the sex-specific nature of adolescent vulnerability to psychiatric conditions is therefore very relevant to the development of prevention and intervention strategies appropriate for both men and women.

Keywords: Sex Differences, Adolescent Development, Amphetamine, Guidance Cues, Cognition

Disclosure: Nothing to disclose.

W282. Time-Of-Day Governs Behavioral and Mesolimbic Dopamine System Response to Rewards and Reward Predictive Cues

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Background: Environmental stimuli paired with rewards can, over time, become associated with the reward and acquire incentivizing properties to motivate reward seeking. Reward-associated cues can have heightened motivational value potentially leading to substance use initiation and addiction relapse. Mesolimbic dopamine signaling plays an essential role in encoding reward-associated cues. The magnitude of dopamine release in the nucleus accumbens (NAc) is modulated by a number of intrinsic and extrinsic factors. An important intrinsic modulator of dopamine release is cholinergic interneurons (CINs). Both burst firing and pauses in CIN firing can govern dopamine release via nicotinic acetylcholine receptors (nAChR). Extrinsically, the dopamine system is modulated by light/dark cycles and time-of-day. Although evidence supports that diurnal variation exists in some parameters, little research has been dedicated to determining the diurnal differences in rapid dopamine and CIN signaling that is critical for learning, motivation, and reward as well as showing a mechanistic link between diurnal shifts in motivated behavior / reward seeking. Our central hypothesis is that there are times within the day that an individual will exhibit increased sensitivity to both the learning of reward-cue associations and cue-incentivized motivation that will lead to time-of-day variation in drug seeking and conditioned behaviors. This variation is mediated by diurnal variations in the CIN/nAChR modulation of rapid DA signaling in the NAc.

Methods: To address this hypothesis, we used male Sprague-Dawley rats (N = 40 – 50) to investigate diurnal variation in both baseline and nicotine-induced facilitation of incentive motivational value towards reward-associated cues using pavlovian conditioned approach (PCA) task. Rats were habituated to a 12:12 light/dark cycle and then trained and performed the PCA task either during the midpoint in their dark (zeitgeber time 18 (ZT18)) or light cycle (ZT6). Rats performed the PCA task for seven consecutive days, after which, rats were euthanized for ex vivo fast scan cyclic voltammetry (FSCV) or used for in vivo FSCV at the same time that they would have performed PCA in order to assess the magnitude of both DA and CIN signaling in the NAc core. For ex vivo FSCV, a bipolar stimulating electrode and carbon fiber recording electrode were proximally placed within the NAc core. Dopamine release to single pulse electrical stimulation (350 uA) was allowed to stabilize before increasing to a series of five pulse stimulations at 5, 10, 20, and 100 Hz. Once baseline (drug-free) stimulations were recorded, we switched back to single pulse stimulation and applied various nAChR compounds, including nicotine (500 nM), the nAChR antagonist, mecamylamine (2 uM), and the nAChR Beta2 subunit-selective antagonist, dihydro-beta-erythroidine (500 nM). Once dopamine peak height to single pulse stimulation stabilized with drug, we repeated the stimulation patterns described above. For in vivo FSCV, rats were anesthetized with urethane during ZT6 or ZT18 and the recording and stimulating electrodes were surgically implanted in the NAc core and ventral tegmental area (VTA), respectively. Dopamine release magnitude elicited from electrical stimulation (30 pulse, 60 Hz) of the VTA was recorded in the NAc.

Results: Rats in their dark cycle exhibited greater sign-tracking (higher reward-associated lever/light cue contacts) in a PCA task compared to rats in their light cycle. Additionally, systemic nicotine facilitates conditioned approach only during the dark cycle. Animals were not sleeping and engage the task during their light cycle since reward (sugar pellet) consumption was no different across light cycle. Ex vivo voltammetry data demonstrates that the ratio of dopamine bursts compared to tonic/background release was amplified with nicotine only in the dark cycle, which corresponds with the robust increase of sign-tracking observed after a nicotine injection in rats in their dark cycle. Note that this desensitizing dose of nicotine (500 nM) decreased dopamine release in the NAc core at lower frequencies that model tonic firing in both cycles (less than 20 Hz) but returned to baseline at higher frequencies that model phasic firing (20 Hz or greater) only in the dark cycle. In vivo voltammetry data demonstrates that differences between phasic dopamine release dynamics are even greater between dark and light cycle. Indeed, phasic bursts of dopamine from VTA stimulation were three times greater in dark cycle animals compared to animals in their light cycle.

Conclusions: Our experiment demonstrates that rats in their dark cycle, but not light cycle, exhibit enhanced dopamine release to frequencies that model phasic firing of dopamine neurons and corresponding conditioned approach behavior that relies on dopamine release from phasic firing in the NAc core. Moreover, nicotine facilitates conditional approach and incentive motivation to reward-predicting cues only in the dark cycle These novel data will enhance our understanding of the neurobiology that underlies heightened motivational states and the degree to which reward-associated cues drive reward seeking. Exploring the dynamic circadian rhythms, as opposed to a single times-of-day, of neural substrates for these behaviors will form a more coherent understanding of vulnerabilities to addiction and other neuropsychiatric diseases and inform potential diurnal variation in the efficacy of treatment strategies.

Keywords: Dopamine, Circadian, Conditioned Cues, Nicotinic Receptors, Acetylcholine

Disclosure: Nothing to disclose.

W283. An Amygdalar Neural Ensemble Encoding the Unpleasantness of Pain

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Background: Pain is a sensory and affective experience. An unpleasant percept dominates the

affective dimension of pain, which provides a motivational drive to initiate protective behaviors that limit exposure to noxious stimuli. While detailed mechanisms underlying the sensory detection of noxious stimuli and spinal processing of nociceptive information have been uncovered, it remains unclear how brain circuits transform this emotionally inert information into an affective pain perception. Injury-induced plasticity within affective circuits, such as the basolateral amygdala (BLA), may lead to a miscoding of sensory information concomitant with the emergence of chronic pain.

Methods: To identify the principles of nociceptive information coding in the BLA, we used a head-mounted miniature microscope paired with viral expression of the Ca2 + indicator GCaMP6m to monitor the activity dynamics of individual BLA neurons in freely behaving mice presented with a diverse set of painful and innocuous stimuli. Concurrently, to monitor pain affect, we developed a method for objectively quantifying aversive behaviors evoked by noxious stimuli. This method categorizes and distinguishes reflexive withdrawal from the temporally delayed, non-stereotype protective responses that indicate an aversive pain percept, such as attending to the painful tissue and adoption of an active escape. Furthermore, we tracked the longitudinal dynamics of BLA neural coding in mice before and after the development of neuropathic allodynia from a peripheral nerve injury (9,777 cells during 73 sessions over 3 months).

Results: We found that prior to nerve injury, multidimensional and population vector analysis of sensory-evoked Ca2 + transients revealed that a unique nociceptive neural ensemble in the

basolateral amygdala, distinct from positive valence ensembles, encodes a diverse array of painful stimuli are encoded. Silencing of this ensemble alleviated pain affective-motivational behaviors without altering the detection of noxious stimuli, withdrawal reflexes, anxiety, or reward. After the establishment of neuropathic pain, the neural ensemble representations of prior innocuous and noxious stimuli became more similar.

Conclusions: Collectively, our results identify a neural representation of nociception in the

amygdala that is necessary for the instantiation of the negative affective qualities of acute and

chronic pain, possibly contributing to pathological psychological co-morbidities such as depression.

Keywords: Pain, Opioid, Miniscope, Amygdala, Avoidance

Disclosure: Nothing to disclose.

W284. Dopamine is a Primary Reinforcing Stimulus That Signals the Probability of its Own Availability

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Background: Dopamine (DA) transmission in the nucleus accumbens (NAc) facilitates appetitive behavior and learning about cues predicting access to reinforcing stimuli. Accordingly, the ability to increase accumbal DA concentrations allows stimuli such as food or addictive drugs to function as goals and for predictive cues to promote goal-seeking. DA release dynamics that drive reinforcement and reward learning are traditionally ascribed to the activity patterns of dopaminergic neurons projecting rostrally from the ventral tegmental area (VTA). This is supported by findings that unexpected rewards elicit burst firing in VTA DA neurons and this response transfers to predictive cues as cue-reward associations are learned. However, because NAc DA release and reinforcement are dissociable from VTA neuronal firing, the degree to which DA neuron activation drives terminal DA release that accompanies reward seeking behavior is not clear. Moreover, whether driving DA neurons artificially is indeed sufficient to promote release that accompanies learning about antecedent cues remains unknown.

Methods: Here, we used fast-scan cyclic voltammetry (FSCV) to measure real-time changes in NAc DA release dynamics while mice worked to receive optogenetic activation of VTA DA neurons (intracranial self-stimulation, ICSS). Male and female mice (3-6 months old; n = 16, estimated on power = 0.9; alpha = 0.5; two-tailed and an expected difference 50% greater than the observed standard deviation) with a heterozygous knock-in of Cre recombinase under the control of the regulatory elements of the DA transporter gene (DAT::Cre + /- mice) were obtained from Jackson Laboratories. Here, we report all FSCV measures in current (nA) as this is the unit of measurement that serves as an estimate of the change in concentration. Principal component regression (PCR) analysis was used to statistically extract the DA component from the voltammetric recording. Training sets were created using non-contingent optogenetically-evoked DA signals obtained following a recording session and a standard set of five basic pH shift voltammograms. For continuous ICSS experiments, FSCV signals were compared to the residual (Q) values obtained from the PCR analysis during 10 s windows normalized to stimulation onset and were included in the analysis when residuals across the 10 s trace fell below the 95% confidence interval (i.e., Qα). Behavioral and voltammetric measures were analyzed using either the Kruskal-Wallis ANOVA on ranks or One-way repeated measures (RM) ANOVA. Tukey's post hoc test was used to correct for multiple comparisons. Statistical analyses were performed in Prism and STATISTICA.

Results: Our findings demonstrate that NAc DA release is inversely related to optogenetic DA neuron activation and to the rate of reinforcement. Additionally, the amplitude of NAc DA release evoked by cues predicting access to optogenetic stimulation varies according to the predictability but not the value of DA neuron activation, when this is used as a primary reinforcer.

Conclusions: This work clarifies how NAc DA release tracks appetitive responding and associative learning specifically when VTA DA neuron activity works as an unconditioned reinforcing stimulus; e.g., when the pursuit of reward is reduced to its minimal neural elements.

Keywords: Dopamine, Voltammetry, Accumbens, Optogenetics

Disclosure: Nothing to disclose.