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T1. Structural Covariance Network Stability Over Time After Trauma Exposure: Preliminary Assessment of Longitudinal Multimodal MRI Data From the Aurora Study

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Background: The structure of human neural circuits is critical for neurocognitive processes that maintain healthy emotional function. Prior human and animal model research suggests that trauma/stress exposure can trigger maladaptive processes that may lead to brain structure changes that contribute to posttraumatic dysfunction. However, limited work to date has investigated how changes in brain structure over time relate to changes in posttraumatic symptoms. Further, prior research has largely used unimodal approaches which do not take into account shared variability between brain measures (i.e., noting that brain gray and white matter likely covary). Therefore, the present study utilized longitudinal multimodal magnetic resonance imaging (MRI) to investigate potential changes in structural covariance networks.

Methods: Participants were recruited from emergency departments following trauma exposure (primarily motor vehicle collisions) as part of the AURORA Study, a multisite longitudinal investigation of posttraumatic syndromes. In the current analysis, an initial dataset of 363 participants completed MRI scans within a) ~2-weeks, b) ~6-months, or c) both ~2-weeks and ~6-months post-trauma. Following quality control and removal of participants missing scan modalities, $n = 248$ participants were included in a multimodal data fusion analysis with $n = 54$ scanned at both timepoints. Structural MRI processing through a combination of FMRIPPREP and FSLVBM was completed to obtain measures of gray-matter volume (GMV), cortical thickness (CT), and pial surface area (PSA) to index gray matter properties. Diffusion tensor imaging was completed to obtain measures of fractional anisotropy (FA), mean diffusivity (MD), and mode of the diffusion tensor (MO) of the white matter skeleton. Data fusion was completed using linked independent components analysis (LICA) of the above brain structure features. A high dimensionality was estimated (d = 119) to better separate participant-specific noise from signal data. LICA returns a participant-specific value for the loading of each component, with each component representing shared variance across the feature modalities. For the 54 participants with longitudinal data, intraclass correlation coefficients (ICC) were obtained to evaluate the stability of the observed components. Preliminary analyses also assessed the relationship between unidimensional posttraumatic syndromes (e.g., PTSD, depression, and anxiety) and component loadings. Analyses of the relationships between changes in component loadings and changes in unidimensional outcome data are planned pending the release of 6-month psychometric data.

Results: ICCs across the components were generally high with 59 of the components demonstrating ICCs of 0.99, but another 44 components showed relatively low ICCs (<0.5). The most reliable component (ICC = 0.999, $p < 0.001$) was a multimodal component of predominantly GMV (26%), PSA (21%), MO (18%) and FA (16%) and was reflective of increased gray matter of the insula, dorsolateral prefrontal cortex (PFC), and ventromedial PFC, and altered white matter of the cingulum, uncinate fasciculus, and inferior longitudinal fasciculus. Interestingly, LICA also separated "noise" from "signal" components, with some of the noise components demonstrating high ICC values (0.95–0.99, $p < 0.001$). These high ICC components reflected participant-specific idiosyncrasies (e.g., distinct patterns of spatial variability) across the modalities. Independent samples *t*-tests of high and low posttraumatic stress severity at 2-weeks post-trauma also revealed differences in two components, with one representing greater GMV (39%) and PSA (53%) of the temporal gyrus and posterior hippocampus [$t(45) = 2.18$, $p = 0.04$; ICC = 0.01, $p = 0.455$] and the other representing greater GMV (49%) and PSA (17%) of the anterior temporal lobe and visual cortex [$t(45) = 2.43$, $p = 0.02$, ICC = −0.22, $p = 0.949$]. High posttraumatic stress severity was associated with lower loadings for both components and the low ICCs suggest these components are highly variable between timepoints, potentially reflecting changes with the process of recovery (to be tested with the release of 6 month data).

Conclusions: Multimodal structural covariance networks assessed in recently traumatized individuals are generally stable between 2-weeks and 6-months following trauma exposure. Participant-specific variance related to time was also identified through LICA and demonstrated high stability. These results suggest participant-specific variance can be readily separated from group-level SCNs that may be related to later posttraumatic outcomes. Preliminary analyses also revealed two SCNs that varied with acute posttraumatic stress symptoms and these networks reflected variability in gray matter properties within regions of the ventral visual stream. Interestingly, our prior work showed an inverse relationship to the one observed here such that greater gray matter properties of the ventral visual stream were associated with greater posttraumatic stress symptoms. These findings may be related to differences in when MRI data was assessed given the low stability of loadings from these components over time. Longitudinal assessment of multimodal structural covariance networks may provide important information on structural changes relevant to assessing susceptibility to posttraumatic stress and identifying brain changes associated with changes in symptoms over time.

Keywords: Multimodal Neuroimaging, Trauma Exposure, MRI, DTI, Data Fusion

Disclosure: Nothing to disclose.

T2. Elemental and Configural Threat Learning Bias Extinction Generalization

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Background: Aversive experiences are complex, containing many cues that can be remembered in different ways. How these events are remembered may have important consequences for later threat and safety responses. For example, different cues can be individually associated with an aversive outcome (elemental) or integrated into a holistic context (configural). A bias toward elemental rather than configural representations has been proposed as an etiology for posttraumatic stress disorder (PTSD). However, it remains unclear how these different representations influence later extinction of these threat memories. As extinction is a crucial feature of exposure therapy for PTSD and other anxiety disorders, understanding how different forms of threat learning modulate extinction has significant clinical implications.

Research in rodents has shown that configural threat learning (e.g., tone + light = shock) facilitated extinction generalization – that is, learning the tone was safe (extinction) diminished responses to the light. However, elemental threat learning (tone = shock and light = shock) did not enable extinction generalization (e.g., Durlach & Rescorla 1980; Debiec et al. 2013). Findings regarding whether tone extinction generalized to the full tone + light compound are mixed (Jones et al. 2013; Troisi et al. 2013). Here we assessed whether the type of representation formed for a multi-cue aversive event (configural vs. elemental) would modulate how broadly human participants generalize extinction of component cues.

Methods: Participants ($N = 96$, 58.3% female) completed a three-day threat conditioning experiment designed to facilitate translation of prior work in rodents. On Day 1, participants learned to associate a tone and a colored square with the delivery of a mild electric shock to the wrist (CS+, 73% reinforced). A separate tone and colored square were never paired with shock (CS−). Threat responses were quantified using skin conductance responses (SCR).

For participants randomly assigned to the configural group ($N = 48$), tones and squares were presented together as a "compound" to create a configural representation (i.e., CS+[tone + square] = shock). For participants in the element group ($N = 48$), tones and squares were presented separately (i.e., CS+tone = shock and CS+square = shock). On Day 2, all participants were exposed to the tones without any shocks (cue extinction). On Day 3, participants were presented with tones and squares separately. Following re-extinction of both cues, they were presented with combined tone + square compounds.

Results: We validated that participants in both groups successfully learned threat associations on Day 1 (CS+ > CS−: $F1,93 = 122.95$, $p < 0.001$; Group x CS: $p > 0.25$) and attenuated responses during extinction on Day 2 (differential response [CS+ - CS−] on Day 1 vs 2: $F1,92 = 78.27$, $p < 0.001$; Group x Day: $p > 0.25$).

We tested extinction generalization from the extinguished tone to the non-extinguished square at the beginning of Day 3. Supporting our hypothesis that elemental vs. configural threat learning would modulate extinction generalization, we found a significant Group by Cue interaction ($F1,282 = 4.21$, $p = 0.04$). Participants in the elemental group were significantly more reactive to square (CS+ and CS−) than tone cues ($b = 0.08$ [0.04], $p = 0.022$), but the configural group showed comparable responses ($p > 0.25$). Furthermore, responses across days in the elemental group revealed that tone extinction diminished responses to the tone but not the square CS+ (Day x Cue: $F1,141 = 4.59$, $p = 0.034$). These findings indicate that extinction generalized between cues following configural but not elemental threat learning.

Next, we examined whether extinction would generalize from component cues to the full compound. After extinction of the tone on Day 2, on Day 3 we extinguished both tone and square cues. We then tested responses to the tone+square compound in both groups. Examining all CS+ trials revealed substantial differences in how threat learning influenced responses to the cues and the compound (Group x CS+: $F2,187 = 8.08$, $p = 0.0004$). Unlike the elemental group, the configural group responded more strongly to the compound than either cue (both $p < 0.012$). The configural group continued to respond strongly to the compound CS+ than CS− throughout Day 3 ($F1,420 = 41.37$, $p < 0.001$), showing that compound threat responses were not extinguished. However, the elemental group did not significantly differentiate the compound CS+ and CS− ($F1,429 = 2.03$, $p = 0.15$; Group x Compound: $F1,849 = 13.43$, $p = 0.0003$). Thus, unlike extinction generalization between cues, extinction of component cues generalized to the compound following elemental but not configural threat learning.

Conclusions: These findings demonstrate that configural and elemental learning for an aversive event had opposite effects on the success of later extinction generalization. Whereas learning a configural association enabled extinction of one component cue to extend to the other component cue, extinguishing both component cues separately did not generalize to the full compound. In contrast, learning elemental associations prevented generalization between cues, but extinguishing both cues generalized and attenuated responses to the compound. These results highlight limits of extinction generalization that raise important questions for therapeutic interventions targeting complex aversive experiences.

Keywords: Fear Conditioning and Extinction, Anxiety & PTSD, Fear Generalization, Learning Theory, Cue-Exposure

Disclosure: Nothing to disclose.

T3. Hippocampal Activation During Contextual Fear Inhibition Related to Resilience in the Early Aftermath of Trauma

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Background: Defining early biological markers of posttraumatic stress disorder (PTSD) versus resilience is of high interest, as this will allow for the early identification of individuals at risk and provide more targets for novel interventions. PTSD is associated with impaired fear inhibition and reduced contextual modulation of behavior. The hippocampus is central to context processing and memory, and has been implicated in PTSD both structurally (e.g., Logue et al., 2018) and functionally (e.g. Garfinkel et al., 2014). Our previous work has demonstrated that more hippocampal activation during a response inhibition task after trauma exposure was related to greater resilience (van Rooij et al., 2016) and fewer future PTSD symptoms (van Rooij et al., 2018). In the current study, we sought to extend our previous findings by employing a fear conditioning and contextual extinction paradigm to further determine the role of the hippocampus in resilience and PTSD in the early aftermath of trauma.

Methods: Participants ($N = 28$) were recruited in the Emergency Department shortly after experiencing a Criterion A traumatic event. Two months later they were invited for an MRI scan. At the time of scan, the Connor-Davidson Resilience Scale (CD-RISC) was used to assess resilience. PTSD symptoms were measured with the PTSD symptom scale (PSS) three months post-trauma. A contextual fear conditioning and extinction task was conducted in a 3T MRI scanner. For each participant, two contrasts of interest were created: (1) fear conditioning [CS+ trials > CS− trials] and (2) contextual fear extinction [CS+ old context > CS+ new context]. The primary region of interest (ROI) for the analyses was the bilateral hippocampus, and the bilateral amygdala, ventromedial prefrontal cortex (vmPFC) and dorsal anterior cingulate cortex (dACC) were used as secondary ROIs. Two types of ROI analyses were performed for both the fear conditioning and the contextual fear extinction contrasts: (1) correlation analyses with resilience score (CD-RISC total score) at time of scan, (2) group differences between trauma survivors with and without PTSD at three months, assessed using univariate analyses of variance. Secondary whole brain analyses for these contrasts using a cluster-defining threshold of $p < 0.001$ and $p < 0.05$ FWE-corrected critical cluster size of 45 (determined using the CorrClusTh.m script) were conducted.

Results: During fear conditioning, activation of the hippocampal ROI correlated positively with post-trauma resilience, $r = 0.48$, $p = 0.01$. This correlation remained significant after correcting for gender, age and baseline PTSD symptoms, $r = 0.53$, $p = 0.01$. During contextual fear extinction, individuals who met diagnostic criteria for PTSD three months post-trauma showed less hippocampal activation than those who did not, in both ROI ($t24 = 2.21$, $p = 0.04$) and whole brain ($p < 0.05$, FWE-corrected) analyses. Including age, gender and baseline PTSD symptoms as covariates again resulted in a significant model, $F(4,19) = 4.02$, $p = 0.02$, with hippocampal activation during fear extinction being the most significant factor related to PTSD status at three months, $F(1,23) = 8.40$, $p = 0.009$. Exploratory correlation analyses for PTSD symptom severity at three months also showed a significant negative correlation between hippocampal activation during contextual fear extinction and PTSD symptom score at three months correcting for age, gender and baseline PTSD symptoms, $r = -0.50$, $p = 0.03$.

Conclusions: Greater bilateral hippocampal activation during fear conditioning and contextual extinction was related to post-trauma resilience and the absence of a PTSD diagnosis three months post-trauma, respectively. The current study supports and strengthens prior findings suggesting the importance of hippocampus-dependent context processing as a mechanism for post-trauma resilience versus PTSD risk, which could be a potential mechanistic target for novel early interventions. The current study adds to a growing body of literature on defining biomarkers for PTSD risk versus resilience, which will be essential for the identification of individuals at risk for psychopathology after trauma exposure and to provide early interventions.

Keywords: PTSD, fMRI, Hippocampus, Fear Conditioning and Extinction, Contextual Cue

Disclosure: Nothing to disclose.

T4. Effect of Levonorgestrel on Threat Extinction

Abstract not included.

T5. PTSD Psychotherapy Adaptively Attenuates Amygdala and Insula Resting State Connectivity With Frontoparietal Cortical Nodes

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Background: Exposure-based psychotherapy is a first-line, efficacious treatment for posttraumatic stress disorder (PTSD), but its mechanisms of action are poorly understood. Identifying the neurobiological mechanisms of action of existing efficacious treatments can facilitate the localization of brain-based treatment targets that can be exploited with novel treatment approaches. Resting state functional brain connectivity is a promising metric for identifying treatment mechanisms and bio-signatures of treatment response, as it is easy to acquire and is a widely researched brain metric. The amygdala and insula are limbic brain structures that share numerous structural connections, tend to co-activate during similar behavioral processes, and consistently display abnormal function in individuals with PTSD. As such, they are core structural components of neurocircuitry models of PTSD pathophysiology and are believed to underlie exaggerated emotional and threat reactivity. Prior investigations have observed abnormal resting state functional connectivity of the amygdala and insula in PTSD. The purpose of this investigation was to assess amygdala and insula connectivity changes following exposure-based psychotherapy for PTSD and the relationship of such changes to treatment-related PTSD symptom improvements. The long-term goal is to identify a potential therapeutic neurobiological mechanism for PTSD psychotherapy to further our understanding of how such effective treatments work to promote symptom resolution.

Methods: Individuals ($N = 66$) with a primary PTSD diagnosis participated in a randomized clinical trial of prolonged exposure therapy ($N = 36$) vs. a treatment waiting list ($N = 30$). Resting state functional magnetic resonance imaging (rsfMRI) was completed prior to randomization and 1 month following cessation of treatment/waiting list. Whole-brain blood oxygenation level-dependent (BOLD) responses were acquired. Intrinsic connectivity was assessed, by subregion, in the amygdala and insula, key limbic structures involved in the disorder pathophysiology. Uniform treatment-related changes in amygdala and insula connectivity were identified in a whole-brain conjunction analysis and examined in relation to PTSD symptom change magnitudes. Dynamic causal modeling (DCM) assessed effective connectivity changes amongst areas displaying adaptive, uniform changes in intrinsic connectivity that scaled with PTSD symptom reductions.

Results: The amygdala and insula displayed widespread patterns of primarily subregion-uniform intrinsic connectivity change, including increased connectivity between amygdala and insula; increased connectivity of both regions with the ventral prefrontal cortex, frontopolar, and sensory cortices; and decreased connectivity of both regions with left fronto-parietal nodes of the executive control network. Larger amygdala-frontal connectivity decreases and insula-parietal connectivity decreases were associated with larger PTSD symptom reductions. DCM revealed a treatment-related decrease in the inhibitory effect of this left frontal region on the left amygdala. Larger decreases in left frontal inhibition of the amygdala were also associated with larger PTSD symptom reductions.

Conclusions: PTSD psychotherapy promotes an adaptive functional segregation of top-down and bottom-up brain circuitry, which may reflect a potential therapeutic mechanism and bio-signature of symptom resolution. More specifically, we speculate a reduction in prefrontal inhibition of the amygdala may reflect an adaptive decrease in the need to exert top-down control in a task-free state. These findings provide mechanistic targets that may be utilized as intermediate biological markers to track treatment efficacy and to design novel intervention approaches.

Keywords: PTSD, Psychotherapy, Resting-state fMRI, Randomized Clinical Trial, fMRI Effective Connectivity

Disclosure: Alto Neuroscience: Stock/Equity (Self).

T6. Training Stimulus-Driven Attention to Treat Pediatric Anxiety Disorders

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Background: Anxiety disorders in adult and pediatric populations have been associated with alterations in attention. While a wealth of research has specifically identified threat or fear-related attention biases in anxiety, a growing literature also finds greater stimulus-driven attention, even with emotionally neutral stimuli. The ventral attention network (VAN) may mediate this involuntary capture of attention. Furthermore, pediatric neuroimaging studies have shown altered VAN connectivity at rest in children at high risk for mood and anxiety disorders and increased neural responses to unexpected stimuli in infants of mothers with anxiety disorders. This convergent evidence implicates stimulus-driven attention and VAN activity as potential targets for therapeutic intervention in anxiety disorders. Here, we measured stimulus-driven, goal-directed, and threat-related attention before and after repeated attention training. We utilized a sham-controlled paradigm aimed at reducing the influence of irrelevant stimuli. We tested whether this training program could reduce symptoms in children with anxiety disorders by reducing the magnitude of stimulus-driven attention to salient stimuli. We further used baseline and post-training neuroimaging to test whether changes in related neural networks relate to behavioral and symptom changes.

Methods: These data were obtained as part of a double-blind, sham-training controlled, small ($n = 18$, 12 female; ages 8-12) clinical trial (registered at Clinicaltrials.gov, ID# NCT03790696). Participants met criteria for generalized anxiety disorder, separation anxiety disorder and/or social anxiety disorder as assessed by a semi-structured clinical interview. Participants were allowed to continue SSRI medications while engaged in the study. Anxiety was measured pre-training and at each subsequent session by validated measures (SCARED and PARS) with primary outcome focusing on SCARED parent report. At baseline and post-training sessions, participants performed tasks measuring various aspects of attention, including a dot-probe task (threat bias), box task (stimulus-driven attention), and arrow task (goal-directed attention). Attention training consisted of eight (8) total forty-five (45) minute sessions conducted at twice weekly frequency, aimed at reducing the impact of irrelevant stimuli on attention. In the training task, participants receive a cue about what side of the screen an eventual target will appear on, eventually pressing a button when the target appears. In the active training condition, one to three (1-3) irrelevant boxes appear on the screen while participants wait for the target. In the sham condition, no such irrelevant boxes appear but the task is otherwise unchanged. Participants were randomly assigned to active or sham training. Pre- and post-training fMRI scans recorded neural responses while completing a task that measured stimulus-driven and threat-related attention in a block design.

Results: Across all treatment groups, participants showed significant decreases in anxiety from baseline (t(paired) = 8.632, df = 17, $p < 1.3e-07$). Changes in anxiety were significantly correlated with improved reaction times in a directed attention task ($r = 0.60$, df = 10, $p < 0.038$). There were also significant changes from baseline to post-training sessions in stimulus-driven attention ($t = 3.90$, df = 15, $p < 0.0015$). In a post-hoc analysis, a composite measure of short-delay stimulus-driven attention and longer-delay rebound of attention also significantly correlated with anxiety changes across all subjects ($r = 0.51$, df = 14, $p < 0.044$). In a preliminary analysis comparing pre- and post-training task-based fMRI, greater reductions in anxiety with training were associated with a greater magnitude of activity change within the dorsolateral prefrontal cortex, ventromedial prefrontal cortex, subgenual anterior cingulate, and insula (uncorrected $p < 0.05$).

Conclusions: In a small, preliminary trial, a novel cognitive training regimen was designed to reduce the magnitude of stimulus-driven attention symptoms in pediatric anxiety disorders. We observed decreased anxiety across all participants in both training conditions. The magnitude of change in anxiety was linked to the magnitude of change in reaction time measures during goal-directed attention tasks. Alongside these behavioral changes, the degree of change in anxiety related to altered signaling in key regions of the ventral attention, dorsal attention, and cingulo-opercular networks. These results support the relevance of multiple aspects of attention to anxiety disorders, potentially both as markers of dysfunction and recovery. This work provides a foundation for a future larger-scale clinical study of stimulus-driven and goal-directed attention and their underlying neural networks in the treatment of pediatric anxiety.

Keywords: Anxiety Disorders, Cognitive Training, Ventral Attention Network, Translational Research, Functional MRI (fMRI)

Disclosure: Nothing to disclose.

T7. Imaging Brain Cortisol Regulation in PTSD With a Novel Neuroimaging Target for 11-Beta Hydroxysteroid Dehydrogenase Type 1

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Background: Numerous studies investigating dysregulation of neuroendocrine stress systems in post-traumatic stress disorder (PTSD) have focused on peripheral measures of the stress hormone, cortisol. These previous examinations assume that the major source of glucocorticoid signaling in the brain is peripherally-produced adrenal cortisol that subsequently enters the brain. However, peripheral cortisol enters the brain at a slow rate and may only contribute to approximately 5% of the cortisol in the brain, arguing for a local source of cortisol production in the brain as an important regulator. We conducted a first study to assess a putative marker of brain cortisol regulation in relation to PTSD clinical pathology, with in vivo imaging of the 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1), an enzyme that generates cortisol in the brain. Together with [11C]PBR28 imaging of translocator protein (TSPO) as a microglial marker, this study offers an opportunity to elucidate the brain glucocorticoid mechanisms underlying the pathophysiology and diversity of symptom presentations in PTSD, and to concurrently examine neural stress and neuroimmune dysregulation in PTSD.

Methods: Sixteen individuals with PTSD (8 female; 37 +/− 10 years) and seventeen healthy, trauma-exposed controls (TC: 8 female; 33 +/− 8 years) underwent positron emission tomography (PET) imaging with [18F]AS2471907, a radioligand for 11beta-HSD1. Participants received 93 +/− 14 MBq [18F]AS2471907 as a

bolus injection and were imaged for 180-240 min on the High-Resolution Research Tomograph. Prefrontal-limbic 11beta-HSD1 availability was estimated as [18F]AS2471907 volume of distribution (VT), with nearly all radioactivity uptake representing specific binding, as demonstrated by previous blocking studies. Multilinear Analysis (MA1) with an arterial sampling-generated input function allowed estimation of VT, defined as the equilibrium concentration of radioactivity in tissue to radioactivity in plasma. In a subgroup of individuals with PTSD who had also completed [11C]PBR28 scans ($n = 10$), [18F]AS2471907 VT was examined in relation to [11C]PBR28 VT in a prefrontal-limbic region. Total PTSD severity was assessed on the PET scan day by self-report using the PTSD Checklist (PCL) for the DSM-5. Subscores for threat (re-experiencing and hypervigilance items) and loss (anhedonia and numbing items) were examined as specific symptom dimensions within PTSD. Group-wise difference in prefrontal-limbic 11beta-HSD1 availability was assessed using univariate ANOVA with PTSD vs. TC group as a between-subject factor, and ROI as a within-subject factor for a priori ROIs comprising a prefrontal-limbic circuit—amygdala, anterior cingulate cortex (ACC), hippocampus, ventromedial prefrontal cortex (vmPFC). A general linear modeling approach was used to compare prefrontal-limbic 11beta-HSD1 availability (a composite average of VT in these a priori ROIs) with the association with overall PTSD severity, threat and loss symptoms, 90-min averaged plasma cortisol, and prefrontal-limbic TSPO availability (adjusting for rs6971-conferred medium- vs. high-affinity binding status).

Results: 11beta-HSD1 availability in a prefrontal-limbic circuit was significantly higher (approximately 16%) in the PTSD compared to TC group (b = 1.16, $p = 0.0057$). Mean 11beta-HSD1 availability in the PTSD group was 29% higher in amygdala, 25% in ACC, 9% in hippocampus, and 17% in vmPFC. Lower prefrontal-limbic 11beta-HSD1 availability was related to greater overall severity ($R2 = 0.27$, $p = 0.038$), and greater threat ($R2 = 0.35$, $p = 0.015$) and loss symptoms ($R2 = 0.39$, $p = 0.010$), within the PTSD group. 11beta-HSD1 availability was not correlated to plasma cortisol levels ($p = 0.37$). There was a significant positive association between prefrontal-limbic 11beta-HSD1 and TSPO availability ($R2 = 0.72$, $p = 0.012$), and a significant main effect of greater 11beta-HSD1 availability being associated with TSPO availability (b = 4.40, $p = 0.039$), after adjusting for [11C]PBR28 binding status.

Conclusions: Overall, 11beta-HSD1 availability in a prefrontal-limbic circuit was higher in the PTSD group. Somewhat contrary to our hypothesis, however, we observed that higher prefrontal-limbic 11beta-HSD1 availability was related to lower overall severity of PTSD symptoms. Additionally, higher 11beta-HSD1 availability was associated specifically with lower threat and loss symptoms, but not with other specific PTSD symptom dimensions. Thus, rather than being a driver of worse symptomatology and brain cortisol dysfunction, the higher 11beta-HSD1 levels observed in the PTSD group may represent an adaptive compensation associated with less severe PTSD symptoms. Importantly, the lack of an association between 11beta-HSD1 and baseline peripheral cortisol levels suggests that 11beta-HSD1 availability may predict symptom dimensions independently of peripheral cortisol. The positive association of higher 11beta-HSD1 with higher TSPO availability, and each respectively with lower PTSD severity, raise the possibility that greater traumatic stress-related brain glucocorticoid signaling may sensitize microglia allowing for a neuroprotective neuroimmune response that results in less severe PTSD symptoms. These findings represent the first steps toward greater understanding of the brain cortisol system in vivo in PTSD and pave the way for future interrogations of this system.

Keywords: PTSD, PET Imaging, TSPO and [11C]PBR-28 PET, Cortisol, HPA Axis

Disclosure: Nothing to disclose.

T8. Psychometric Associations Between Negative Urgency and Anxiety-Based Avoidance

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Background: Anxiety disorders are highly prevalent, with global estimates at approximately 7.3% in adults (Stein et al., 2017), and impair functioning in multiple domains (Kessler et al., 2005). Anxious distress leads to behavioral avoidance, which recursively perpetuates anxiety symptoms and further impairs social, occupational, and educational functioning (Klumpp et al., 2013). The current conceptualization of anxious avoidance neglects individual differences in anxious presentations that might be more consistent with externalizing symptoms, and more specifically, trait impulsivity. Trait impulsivity has been commonly linked with externalizing disorders (Brooks et al., 2017) and considered opposite anxious avoidance (Barratt, 1965; Moustafa et al., 2017). Recent findings suggest that co-occurring presentations of high anxiety and high impulsivity may underlie clinical disorders across internalizing and externalizing spectrums. However, due to broad conceptualizations of impulsive behavior, it remains unclear whether anxiety could be positively associated with global impulsivity or specific facets of impulsivity. Negative urgency (NU), defined as rash behavior specifically enabled during negative emotional states (Um et al., 2019), may provide common ground to examine the overlap between high anxiety and high impulsivity.

Methods: 250 adults in the United States (Mage = 31.32 SDage = 5.35) were recruited through Amazon Mechanical Turk to complete self-report questionaires regarding global (Barratt Impulsiveness Scale-11; BIS-11; Patton, Stanford, & Barratt, 1995) and dimensional (The Urgency, Premeditation, Perseverance, Sensation Seeking, and Positive Urgency Impulsive

Behavior Scale; UPPS-P; Whiteside & Lynam, 2001) impulsivity including trait-level NU. Participants also completed measures of trait and state level anxiety symptoms (The State Trait Anxiety Inventory; STAI; Spielberger, Lushene, & Jacobs,1983), and experiential avoidance (Acceptance and Action Questionnaire – II; AAQ-II; Hayes et al., 2004). Total raw scores for the BIS-11 and AAQ-II, and subscale scores of the UPPS-P and STAI were calculated for analyses. The primary subscale of interest for the UPPS-P was the NU subscale, and the primary subscale of interest for the STAI was the trait subscale.

Results: In a preliminary mediation path model the path from trait anxiety to NU was statistically significant ($\beta = 0.47$; 95% CI: 0.47, 0.65), as was the path from NU to experiential avoidance ($\beta = 0.36$; 95% CI: 0.12, 0.20). The indirect effect was small to moderate in size, and statistically significant (indirect effect = 0.17; 95% CI: .05, 0.12).

Conclusions: Preliminary findings suggest that NU may mediate the relationship between trait anxiety and experiential avoidance. The unique construct of NU may provide a conduit between anxiety and impulsivity that will allow for a more granular study of their neural and behavioral similarities and distinctions. Future analyses will include global impulsivity and other dimensional subscales of impulsivity to more specifically understand the relationships between facets of impulsivity and anxiety-based avoidance. Future directions will also include the analysis of these relationships using psychometric and neuroimaging data from the Adolescent Brain Cognitive Development (ABCD) Study to explore shared and distinct aspects of inhibitory control that may underlie emotional reactivity and motor inhibition.

Keywords: Anxiety, Impulsivity, Internalizing Disorders

Disclosure: Nothing to disclose.

T9. Amygdalostriatal Transition Zone Circuits Mediating Associative Learning and Motivated Behaviors

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Background: The ability to respond appropriately to stimuli that predict rewards or punishments lies at the core of evolutionary fitness, and is disrupted in a number of neuropsychiatric disease states. Despite the overwhelming consensus that the amygdala is important for mediating associative learning, bilateral loss-of-function manipulations of the lateral amygdala (LA), basolateral amygdala (BLA) and central nucleus (CeA) still result in substantial residual behavioral responses to conditioned stimuli which are currently unexplained by any existing conceptual framework. Although relatively unexplored, the amygdalostriatal transition zone (ASt) is situated to act as a parallel circuit which mediates associative learning to direct behavior. Like the amygdala, the ASt receives converging sensory input from the thalamic and cortical pathways. However, the downstream projections of the ASt are distinct from the canonical outputs of the amygdala complex, and are integrated with striatal circuits involved in action selection. Despite this intriguing circuit connectivity the function of the ASt is almost completely unknown, resulting in a major gap in our knowledge of circuits underlying motivated behaviors.

Methods: To investigate the role of the ASt in associative learning and motivated behaviors, we first examined the behavioral effects of unilateral activation of the excitatory opsin ChR2 targeted to the ASt ($N = 8$ mice ChR2, 10 mice eYFP). We then quantified the genetic identity of neurons in the ASt, dorsal striatum (DS) and tail of striatum (TS) using RNAscope labelling targeted to dopamine receptor 1 (drd1a, 'D1+') and dopamine receptor (drd2, 'D2+') ($N = 8$ mice, 16 sections ASt, 8 mice, 12 sections DS, 8 mice, 12 sections TS). We used in vivo electrophysiology to examine changes in ASt neuron responses to conditioned stimuli predicting aversive foot shocks in a Pavlovian fear conditioning paradigm ($N = 5$ mice, 22 neurons paired group, $n = 3$ mice, 21 neurons unpaired group), as well as responses to distinct conditioned cues predicting aversive and rewarding stimuli ($N = 6$ mice, 49 neurons). ¬To examine neural activity in D2+ ASt neurons, we used in vivo miniscope imaging to record changes in GCaMP7f fluorescence in response to cues predicting aversive and rewarding stimuli (Preliminary data, $n = 39$ neurons). Finally, to determine if D2+ ASt neuron activity was necessary for behavioral responses to conditioned stimuli, we targeted D2+ neurons with the inhibitory opsin NpHR, and examined the effects of reversibly inhibiting these neurons on responses to aversive and rewarding stimuli during a two-tone discrimination task ($N = 5$ mice NpHR, 6 mice eYFP).

Results: Our data showed that unilateral optogenetic activation of ChR2-expressing ASt neurons was sufficient to drive robust freezing behavior (83% increased freezing in ChR2 group vs. −2% in eYFP controls; $p = 0.0015$, unpaired *t*-test) and real-time place avoidance of areas paired with stimulation (32% reduction of time in 'ON'side vs. eYFP controls during last 10 min; $p = 0.012$ unpaired *t*-test). We also found that the ASt has a significantly greater proportion of D2+ ASt neurons than both the dorsal striatum and tail of striatum (Chi-square test, $p = 0.0010$ ASt v. DS, $p = 0.0081$ ASt v. TS). Our in vivo electrophysiological recording data demonstrated that following Pavlovian fear conditioning, ASt neuron responses to a shock-predicting cue were significantly greater in 'paired group' mice compared with 'unpaired group' controls where cues and shocks were explicitly unpaired (Repeated measures ANOVA, Effect of Group $p = 0.028$). Additionally, our preliminary calcium imaging data suggest that D2+ ASt neurons also show increased conditioned cue responses following fear conditioning. Finally, in loss-of-function experiments we found that optogenetic inhibition of D2+ ASt neurons caused a striking reduction in conditioned behavioral fear responses to a shock-predicting cue (51% decrease in freezing, $p = 0.00086$, paired *t*-test).

Conclusions: Our study provides the first demonstration that ASt neurons are sufficient to drive robust freezing and avoidance behaviors, and undergo conditioned changes in responsiveness to cues which predict aversive stimuli. Additionally, we show that the ASt contains a higher proportion of D2+ neurons than other regions of the striatum, and that inhibition of these D2+ neurons results in a significant reduction in fear response (conditioned freezing) to cues predicting aversive stimuli. Consequently, we believe that the ASt may be an overlooked and critical structure that contributes to conditioned behavioral responses to stimuli.

Keywords: Amygdala, Striatum, Associative Learning, Pavlovian Conditioning, Auditory Fear Conditioning

Disclosure: Nothing to disclose.

T10. The Effect of Early Life Racial Discrimination Experiences on Adult Maladjustment and Accelerated Aging for African Americans: Exploring the Moderating Role of Socioeconomic Advantage and Disadvantage

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Background: Researchers have suggested that early life exposure to psychosocial stressors may influence negative affective states (e.g., depression) and other adjustment related factors across the lifespan (e.g., self-control and self-confidence). These experiences also have effects on poor physical health through physiological dysregulation and increased wear and tear on body systems over time. An early and pervasive stressor related to mental and physical health for African Americans (AA) is racial discrimination. Although a growing literature has examined the effects of early life stress related to racial discrimination on adulthood health, very limited research has examined how socioeconomic status (SES)/contextual factors could influence this process. Utilizing a biopsychosocial framework, an important step in research it to examine the role of SES in the link between racial discrimination, maladjustment, and accelerated aging.

Methods: This study examined the role of adult maladjustment (depression, self-control, and self-confidence) in mediating the relationship between early life experiences of racial discrimination and accelerated aging in adulthood for AA (i.e., prediction over a 19-year period; from age 10 to 29). This study also examining the moderating role of SES in the racial discrimination-maladjustment link. The sample included 368 AA participants from the longitudinal Family and Community Health Study.

Results: Our study found a significant indirect effect of racial discrimination on aging through young adult maladjustment (age 20-29; $\beta = 0.021$[0.001, 0.057]), accounting for 32% of the total variance. We also found that SES significantly moderated the association between racial discrimination and adult adjustment. Interestingly, this led to a greater (and significant) indirect effect of discrimination on aging among those raised in higher SES households (i.e. those at lower SES risk). Chi-square = 1.327, df = 2, $p = 0.5151$; CFI = 1.000; RMSEA = 0.000. Gender, education, age, healthy diet, exercise, sleeping, smoking, and alcohol consumption are controlled in these analyses.

Conclusions: These findings support research that early life stress due to racial discrimination lead to negative mental health outcomes continuing into young adulthood that confer risk for accelerated aging, and possibly premature disease and mortality

in AAs. Particularly the results related to SES have implications for future research and potentially targeted clinical and culturally-responsive interventions.

Keywords: Racism, Accelerated Aging, African Americans, Socio-Economic Status

Disclosure: Nothing to disclose.

T11. A Randomized Double-Blind, Placebo-Controlled, Pilot Trial of Mirtazapine for Anxiety in Children and Adolescents With Autism Spectrum Disorder

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Background: Comorbid anxiety disorders affect 40–70% of youth with autism spectrum disorder (ASD). Untreated anxiety in youth with ASD is associated with increased aggression, poor social functioning, and more severe symptoms of ASD. Mirtazapine is a central presynaptic α2-adrenergic antagonist which increases both serotonin and norepinephrine at the neuronal synapse and is a post-synaptic 5-HT2A, 5-HT2C, and 5-HT3 serotonin antagonist. It is used in clinical practice for the treatment of depression and anxiety in adults. Retrospective and open-label data have demonstrated that mirtazapine may be effective for treating anxiety in youth with ASD. Double-blind, placebo-controlled studies on the pharmacologic treatment of anxiety in youth with ASD are lacking. The aim of this study was to conduct a pilot trial of mirtazapine for the treatment of anxiety in youth with ASD.

Methods: This study was a 10-week randomized, double-blind, placebo-controlled trial. Study participants were youth ages 5 to 17 years with ASD and clinically significant anxiety (Pediatric Anxiety Rating Scale [PARS] score ≥ 10). All subjects had an abbreviated IQ ≥ 50 on the Stanford Binet, Fifth Edition. Participants were diagnosed via clinical interview completed by a board-certified child and adolescent psychiatrist experienced in providing clinical care to youth with ASD, based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria, and corroborated by the Autism Diagnostic Interview-Revised administered by research reliable raters. Subjects with a diagnosis of Rett's disorder, childhood disintegrative disorder, obsessive-compulsive disorder, posttraumatic stress disorder, major mood disorder, psychotic disorder, or substance use disorder were excluded. The participants were randomized to mirtazapine or matching placebo in a 2:1 ratio. Participants were treated for up to 10 weeks with mirtazapine (7.5–45 mg/day) or placebo. The co-primary outcome measures were the PARS and the Clinical Global Impressions-Improvement subscale (CGI-I). Secondary outcome measures included the Screen for Child Anxiety Related Disorders, Child and Adolescent Symptom Inventory Anxiety Items, Aberrant Behavior Checklist, Children's Sleep Habit Questionnaire, Clinical Global Impressions-Severity subscale, and Developmental Disability-Child Global Assessment Scale. The study was designed to have 80% power to detect a standardized effect size of 0.7 for 10-week change in clinical outcomes for mirtazapine and a standardized effect size of 1.1 for differences in 10-week change in clinical outcomes between mirtazapine and placebo.

Results: Thirty participants were randomized (mirtazapine = 20, placebo = 10). One participant assigned to mirtazapine withdrew after six weeks of study participation due to symptoms of irritability and aggression. The remaining 29 participants completed the full 10-week treatment period. Children assigned to mirtazapine experienced a significant decrease on all the anxiety measures including the PARS (ES 1.76, $p < 0.001$) which was a co-primary outcome measure. Forty-seven percent of the participants assigned to mirtazapine (95% CI 22%: 74%) and 20% of the participants assigned to placebo (95% CI 2%: 60%) were rated as "much improved" (CGI-I = 2) or "very much improved" (CGI-I = 1) for anxiety, $p = 0.46$. There were no statistically significant differences in mean 10-week changes between mirtazapine and placebo on any outcome measure. No participants experienced a serious adverse event. The most common adverse effects among participants treated with mirtazapine were sedation/drowsiness (60%) and appetite increase (50%). There were no significant differences in adverse effect frequency between mirtazapine and placebo. There was a statistically significant within-group increase in body mass index (BMI) by 0.7 in the mirtazapine group. There were no statistically significant differences in change in BMI between mirtazapine and placebo.

Conclusions: Subjects treated with mirtazapine demonstrated substantial and statistically significant within-group improvement on all of the anxiety measures, including the PARS (a co-primary outcome). The results support the implementation of a larger randomized controlled trial which is powered to provide more conclusive evidence on the benefit of mirtazapine for anxiety in this population.

Keywords: Autism Spectrum Disorder, Anxiety, Adolescent

Disclosure: Nothing to disclose.

T12. Sex Differences in the Ability to Extinguish Fear in Pre-Adolescent Children

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Background: Pavlovian fear conditioning and extinction paradigms have been widely used to examine the neurobiological basis of fear and anxiety disorders. Studies in adolescents and adults have revealed important sex differences in fear extinction, with females frequently showing poorer extinction as compared to males. This disparity may help to explain the greater reported vulnerability of females than males to anxiety disorders. Poorer extinction recall in female adolescents and adults is thought to be driven by the effects of puberty and sex hormones (e.g., estradiol). It is unclear whether sex differences in fear extinction exist prior to the onset of puberty (i.e., gonadarche; ≈11 yrs in females, ≈12 yrs in males), which may be influenced by other biological factors (e.g., hormonal changes related to adrenarche, genes on X or Y sex chromosomes).

Methods: 22 female and 22 male children (6–11 years), matched on age and pubertal status (77% pre/early pubertal Tanner stage, $t(42) = 0.3$, $p = 0.8$), completed a contextual virtual reality fear conditioning and extinction paradigm. In this paradigm, adult male avatars served as the conditioned stimuli (CS) and conditioning and extinction occurred in separate contexts (i.e., AB design). Conditioned fear was measured throughout the experiment to the fear (CS+) and safety cues (CS−) using skin conductance responses (SCRs). Two sex (male, female) x time (early, late) x CS−type (CS+, CS−) repeated-measures ANOVAs were applied to test for effects of sex on SCRs during fear conditioning and extinction.

Results: There were no significant effects of sex, sex x time (early, late), or sex x CS−type (CS+, CS−) interactions on SCRs during fear conditioning (ps > 0.05). During extinction, however, there was a significant main effect of sex ($F(1,40) = 5.54$, $p = 0.024$), such that overall SCRs were higher among males than females. There was also a significant sex x time x CS−type (CS+,

CS−) interaction (F(1,40) = 4.425, $p = 0.042$) for SCRs. Post hoc analyses showed that this interaction effect was driven by no difference in SCRs to the CS+ vs. CS− among females during early extinction ($p = 0.9$), suggesting poor differentiation between threat and safety cues. Further, among females, SCRs to the CS+ did not differ between early and late extinction ($p = 0.7$), suggesting poor extinction. In contrast, males showed higher SCRs to the CS+ relative to the CS− during early extinction ($p = 0.046$) and demonstrated lower SCRs to the CS+ during late as compared to early extinction ($p = 0.008$), suggesting intact differentiation and extinction, respectively. Importantly, the observed sex differences in extinction to the CS+ (but not in differentiation between the CS+ and CS−) remained significant when excluding five participants who were ages 10-11 and four participants who were more advanced in pubertal status (i.e., mid/late).

Conclusions: Reported sex differences among adolescents and adults during fear extinction are thought to be driven by the onset of puberty and the influence of sex hormones (e.g., estradiol). Here, we unexpectedly observed sex differences in differentiation between threat and safety and the ability to extinguish fear during childhood, when estradiol levels are typically very low. This suggests the presence of other biological factors that may contribute to sex differences prior to the onset of puberty (e.g., hormonal changes related to adrenarche, genes on X or Y sex chromosomes). Importantly, the observed sex differences in fear extinction remained significant when individuals ages 10+ or more advanced in pubertal status were excluded. Interestingly, epidemiology studies suggest that the onset of the first or any anxiety disorder is typically in childhood, prior to the onset of puberty. Further, prior studies suggest that the sexual disparity in anxiety emerges as early as middle childhood. Together, these data point to sex differences in fear extinction during childhood, which is earlier than previously reported, and may contribute to sex differences in risk for anxiety disorders.

Keywords: Fear Conditioning and Extinction, Sex Differences, Anxiety & PTSD, Children

Disclosure: Nothing to disclose.

T13. Activation Mutation in the Ras/MAPK Pathway Alters the Functional Resting-State Architecture Underlining Executive Function and Attention

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Background: Understanding the brain mechanisms underlying ADHD, one of the most prevalent neurodevelopmental disorders, is critical for improving diagnosis and treatment. Progress thus far has been hampered due to genetic heterogeneity and diverse clinical presentation. The study of human genetic models provides a more homogeneous model for disease pathophysiology compared to the study of idiopathic ADHD. Noonan syndrome (NS), a condition caused by genetic mutations activating the Ras/mitogen-activated protein kinases (MAPK) pathway, is strongly associated with ADHD symptoms, including deficits in attention, hyperactivity, and executive function. While basic research demonstrates that the Ras/MAPK pathway is critical for brain development and function, the effects of NS on brain function are unknown. We examined whether NS alters the functional brain architecture underlining ADHD symptomatology.

Methods: We used fMRI to examine resting-state functional connectivity, a summary of synchronous changes in the brain over time that provides quantification of overall functional architecture. Participants (age 4–12 years) included 39 children with NS (mean age 8.44, SD = 2.20, 25 females) and 49 typically developing (TD) children (mean age 9.02, SD = 9.02, 33 females). Participants also completed standardized behavioral measures of attention and executive function.

We performed hypothesis-driven seed-based analyses using seeds in bilateral caudate and putamen, two subcortical regions that demonstrated neuroanatomical differences in our study population. GLM was then used to test for significant group differences within the spatial extent of connectivity between each seed and every other voxel in the brain.

We used data-driven independent component analysis (ICA) to identify eight resting-state networks corresponding to those previously defined in the literature: visual, somatomotor, dorsal attention, ventral attention, limbic, left frontoparietal, right frontoparietal, default mode. GLM was then used to test for significant group differences in connectivity within the entire spatial extent of each network. All reported p-values were corrected using the false discovery rate procedure (FDR).

Results: We included twenty-eight children in the NS group and 46 in the TD group who met strict criteria for MRI data usability and in final analyses.

Seed-based analyses indicated hypoconnectivity for the NS group between left caudate and dorsolateral prefrontal cortex ($p = 0.002$, d = 0.93, power = 0.97), motor ($p = 0.011$, d = 0.74, power = 0.86), and premotor ($p = 0.041$, d = 0.50, power = 0.54) areas and between the right caudate and somatosensory cortex ($p = 0.019$, d = 0.67, power = 0.78). The caudate seed was also associated with hyperconnectivity with anterior cingulate for the NS group ($p = 0.024$, d = 0.58, power = 0.67). We also found hyperconnectivity for the NS group between the left putamen and dorsolateral prefrontal cortex ($p = 0.024$, d = 0.58, power = 0.67) as well as hypoconnectivity between right putamen and subcortical regions ($p = 0.024$, d = 0.61, power = 0.37).

Primary ICA results indicated significant hyperconnectivity for the NS group within visual ($p = 0.003$, d = 0.85, power = 0.94), ventral attention ($p = 0.006$, d = 0.76, power = 0.88), left frontoparietal ($p = 0.024$, d = 0.59, power = 0.69) and limbic networks ($p = 0.002$, d = 0.91, power = 0.96). Post-hoc correlation analysis indicated significant correlations within the NS group between the visual network connectivity and visuospatial ability (NEPSY arrows, r(27) = 0.50, $p = 0.010$) and frontoparietal connectivity and semantic access/production of names (NEPSY speeded naming, r(27) = 0.43, $p = 0.024$). Further, these correlation coefficients were significantly different between NS and controls in the visual network (Fisher's test, z = 2.03, $p = 0.04$) and were not significantly different in the frontoparietal network (z = 1.48, $p > 0.10$).

Conclusions: Overall, we identify the effects of NS on brain functional architecture in subcortical and cortical regions. We observed a striking pattern of hyper- and hypoconnectivity between subcortical regions and the dorsolateral prefrontal cortex, a critical region for executive functioning and cognitive control. In cortical regions, we found that NS was associated with alteration of several large-scale resting-state networks.

The link between altered subcortical volume and functional connectivity with critical frontal executive control regions is an essential step in specifying neurobiological mechanisms that underlie altered executive function and attention symptoms. Hyperconnectivity within the visual, dorsal attention, and left frontoparietal networks may indicate compensatory neural mechanisms within individuals with NS who also have deficits with attention and executive function. Our correlation results demonstrate a significant positive relationship between network connectivity and executive function within visual and frontoparietal networks and further support our hypothesis of NS's compensatory mechanisms.

Together, our results describe a pattern of altered resting-state connectivity that represents an intermediary phenotype between Ras/MAPK mutation and behavior in NS. These results may be useful in designing and measuring responses to behavioral and/or pharmacological therapies for individuals with NS. They may have utility in identifying disorder pathophysiology in subgroups within idiopathic ADHD.

Keywords: ADHD, Resting State Functional Connectivity, Genetic Human Model, Ras/MAPK Pathway

Disclosure: Nothing to disclose.

T14. Safety Signal Induced Elevations in Ventral Hippocampal Activity During Adolescence Can Improve Extinction Learning

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Background: A peak in diagnoses for anxiety disorders occurs during adolescence and earlier onset of psychiatric symptoms is associated with increased symptom severity. Making matters worse, conventional behavioral treatments based on principles of fear extinction have limited long-term efficacy for a notable percentage of the adolescent patient population. Thus, generating a framework for clinical treatments that integrates an understanding of the typical and atypical development of fear circuitry and behavior is crucial to enhancing both the immediate and long-term benefits of treatment during adolescence. To address this, my research investigates processes underlying the acquisition and application of safety signal learning, a form of fear inhibition with high clinical relevance.

Methods: Adolescent (postnatal day, P29) and adult (P70) mice underwent discriminative conditioning during which they were repeatedly presented with fear cues (a tone paired with a footshock) and safety cues (a second tone, no footshock). After acquiring an explicit "safety signal" with conditioned inhibitor properties, mice underwent extinction with a safety signal intermixed ($n = 15$ Adults/16 Adolescents), presented simultaneously ($n = 13/15$) or absent ($n = 15/15$). Rates of extinction and the retention of extinction gains two weeks later were quantified. To investigate how the brain uses safety signals to inhibit fear, in-vivo calcium imaging (fiber photometry) was used to record neural activity in prelimbic-projecting ventral hippocampal neurons (VH-PL) alongside behavior ($n = 14/7$).

Results: Rates of extinction differed by group in adolescents ($p < 0.001$; driven by delayed extinction following intermixed safety exposure) but not adults. Two weeks later, extinction retention differed by group in both adolescents ($p < 0.001$) and adults ($p < 0.03$). While exposure to intermixed safety cues during extinction improved retention in both ages, the magnitude of retained extinction was significantly stronger for adolescents ($p < 0.01$) than adults ($p < 0.07$). Simultaneous fear and safety pairings during extinction did not impact retention for either age. Fiber photometry recordings revealed increases in VH-PL activity across extinction trials, but no age differences. Conversely, while VH-PL also exhibited higher responding to safety cues than fear cues in both ages, the elevation was greater for adolescents ($p < 0.04$).

Conclusions: These findings inform the parameters for when and how safety signals can be used effectively. Notably, mice in the 'intermixed' groups are exposed to half as many fear cues as mice in other groups. Yet, while constant inhibition of fear via a safety signal is not beneficial, alternating presentations of fear and safety cues during extinction can augment fear regulation. This research also addresses a gap in the literature regarding the mechanisms underlying adolescent fear inhibition. Replicating our recently published findings in adults (Meyer et al. PNAS, 2019), using safety signals to inhibit fear during adolescence similarly recruits VH-PL neurons. However, safety signal induced elevations in VH-PL activity apparent specifically during adolescence may confer an advantage for using safety signals to facilitate extinction. Together, these findings have great translational potential for optimizing treatments for pediatric anxiety disorders.

Keywords: Adolescence, Fear Extinction, Ventral Hippocampus

Disclosure: Nothing to disclose.

T15. Association of Choroid Plexus Enlargement With Oligo-Amenorrhea in Adolescents With Low-Weight Atypical Anorexia Nervosa and Anorexia Nervosa

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Background: Despite the important role the choroid plexus (CP) plays in brain homeostasis, it is largely unexplored in psychiatry. The CP consists of a network of capillaries enclosed by a single layer of epithelial cells joined together by tight junctions to form the blood-CSF barrier. The blood-CSF barrier is an active barrier, secreting CSF and transferring metabolites from CSF to blood bidirectionally, and thus, playing a crucial role in communicating inflammatory reactions from the periphery to the central nervous system. Integrity of the CP is crucial for maintaining CSF ion homeostasis and blood-CSF barrier permeability. Enlargement of CP may reflect greater neuroinflammation, as abnormal function of the CP requires greater passage of peripheral inflammation markers to dampen neuroinflammation. These processes are further controlled by various proteins, enzymes and hormones, including sex hormones.

Animal models have shown that decreases in estrogen, a neuroprotective hormone with anti-inflammatory effects in the brain, leads to increased permeability of the blood-brain and blood-CSF barriers. Estrogen serves as a neuroprotective hormone by enhancing inter-endothelial cell tight junction functioning, which is regulated by the CP. Oligo-amenorrhea (infrequent menstruation) due to reduced estrogen is associated with weight loss, malnutrition, and/or abnormal eating seen in restrictive eating disorders (EDs) such as anorexia nervosa (AN) and atypical-AN (at-AN), the latter of whom have similar psychopathology and behavior as AN but maintain higher weights. The CP is understudied in EDs, although one small study reported increased left CP volume in AN compared to healthy controls (HC). Clinical case reports suggest that papillomas of the CP may lead to the onset of AN while resolution of AN cognitions and behaviors follows with its removal.

In this study we aimed to improve our understanding of the relations between CP structure and estrogen in a cohort of females with known EDs (AN and at-AN). We hypothesized that the CP would be larger in patients with AN and at-AN compared to matched HC and that increased CP volume would be associated with less estrogen exposure in AN and at-AN.

Methods: T1 weighted scans from 71 postmenarchal females diagnosed with DSM-5 criteria AN($n = 27$) or atypical-AN($n = 19$) and 25 age-matched HCs were parcellated with FreeSurfer to determine CP volume. Estrogen exposure was calculated as the number of months with endogenous estrogen exposure over the previous 9 months as determined by menstrual history. We ran pairwise contrasts using ANCOVA to assess CP volume in AN, at-AN, and HCs and partial correlations for estrogen exposure and CP. All analyses were corrected for multiple comparisons using the false discovery rate. CP volume was adjusted for total intracranial volume (TIV) and age in all models. To examine whether CP

volume was influenced by total lateral ventricle volume (LV) or total gray matter (GM) volume, we re-ran all group comparisons using total lateral ventricle volume and total lateral ventricle volume plus total GM volume instead of TIV as covariates to regress out the effects of cortical atrophy and ventricular enlargement.

Results: Left CP volume was significantly larger in AN(M = 502.3, SD = 118.7) and at-AN(M = 564.9, SD = 164.2) compared with HC(M = 443.6, SD = 115.9) (f = 9.9, $p < 0.001$). There was no significant difference between AN and at-AN in the left or right CP. No differences in right CP were observed between at-AN, AN, and HC (f = 0.36, $p = 0.7$). When including lateral ventricle volume or total lateral ventricle volume plus total GM volume instead of TIV as a covariate, volumes of the left CP remained significantly larger in the AN and at-AN groups than the HC group. In individuals with at-AN and AN, left CP volume was negatively associated with endogenous estrogen exposure (R = −0.43, $p = 0.002$). There were no significant relationships between estrogen exposure and the CP in HC. Total GM volume was not significantly associated with the left or right CP in at-AN, AN, or HC.

Conclusions: We found that left CP volume was significantly higher across the AN spectrum (AN and at-AN) compared with HC (independent of total GM volume), and inversely associated with endogenous estrogen exposure in AN. Our results support our hypothesis that CP enlargement exists in AN and at-AN and is related to decreases in estrogen exposure in adolescents. Further, the laterality observed in the current study replicates the one other study reporting associations between AN and CP, which also found increased volume in only the left CP. Asymmetry of the CP may represent an early marker of pathology, as enlargement of left CP relative to right CP, is the earliest brain asymmetry identified thus far (noticeable at 11 weeks post conception) and is distinct from other brain structures in terms of their overall transcriptomic profile(genes involved in cell-adhesion and immune responses more highly expressed in left CP). Disruptions in estrogen exposure in adolescents with AN may lead to increased blood-brain-barrier (BBB) permeability and should be further explored using more direct measures of BBB (such as CSF collection). While this currently represents the largest study of CP volume in AN, replication across cohorts will be necessary. Longitudinal studies administering estrogen will be important in determining whether estrogen normalizes CP volume and in turn, ED psychopathology.

Keywords: Anorexia Nervosa, Structural MRI, Choroid Plexus, Estrogen Synthesis

Disclosure: Nothing to disclose.

T16. Frontolimbic Gene Expression Signatures for Lifetime Illness and Survival in Years

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Background: The human brain epitomizes the evolutionary adaptation to survive environmental and social challenges over a lifetime. Previous brain lesions, neuroimaging, and cellular brain studies have identified a distributed frontolimbic brain network encompassing the subgenual cingulate and insula in supporting the perceptual, mnemonic, and experiential aspects of interoception, emotion, and memory. The cingulate-insula network enhances survival by integrating i) interoceptive (i.e., inner bodily states), with ii) exteroceptive (i.e., outer bodily percepts) sensory domains. This brain network synthesizes inner and outer sensory worlds by making sense of how external sensory events (i.e., visual; auditory; olfactory; tactile/motor; gustatory) impact the observers' internal sensory (i.e., homeostatic and affective feeling states). However, the molecular signatures for the interoceptive-exteroceptive cortex in relation to lifetime mood dysfunctions and survival is unknown.

Methods: Here, we phenotyped the mental illness status and survival rate (i.e., age at death and lifetime physical health status) in a postmortem sample and extracted RNA from the subgenual cingulate ($N = 72$) and anterior insula ($N = 72$) in all donors. To identify gene expression signatures related to mental illness status and survival rate, we performed differential gene expression analysis while controlling for RNA integrity scores. Pathways enriched among the differentially expressed genes were identified to understand the functional dysregulations associated with our primary outcome measures.

Results: In a postmortem donor sample of 24 bipolar disorder (6 females), 24 major depressive disorder (8 females) and 25 controls (8 females), the survival rate correlated with the degree of comorbid physical illness status ($r = 0.62$) but not with the degree of comorbid mental illness status ($r = -0.02$). Pathway analysis identified significant associations between metabolic pathway dysregulations and mental illness status, as well as bodily homeostatic pathway dysregulations and survival rate in subgenual cingulate gene expression using Bonferroni corrections. Similarly, associations between immune and inflammatory pathway dysregulations and mental illness status and between cellular and neurodevelopmental pathway dysregulations and survival rates were identified in anterior insula gene expression.

Conclusions: Our results uncovered a molecular profile of the subgenual cingulate and anterior insula cortex in dysfunctions related to lifetime mental illness status and bodily homeostatic processes in mood disorders. Further multidisciplinary studies in larger samples are required to validate the observed molecular processes influencing the mental and physical health.

Keywords: Subgenual Anterior Cingulate, Gene Expression, Anterior Insula, Mood Disorders, RNA-Sequencing

Disclosure: Nothing to disclose.

T17. Effect of Chronic Restraint Stress on Maternal Behavior and Underlying Neural Circuitry in Mice

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Background: Stress is a risk factor for development of Postpartum mental illnesses including Postpartum Depression, Postpartum Anxiety, and other disorders. In the United States, these disorders can affect up to 20% of mothers and 10% of fathers annually. In this study, we will take advantage of chronic restraint stress which has been shown to significantly decrease parental behavior in both naive and lactating female mice to study the impact on neural circuitry related to maternal behavior.

Methods: In a first set of experiments, we subjected naive adult female mice (C57BL/6) to chronic restraint stress in a perforated 50 mL conical tube for 1 hour per day for 20 days or as a control daily handling and weighing ($n = 9$ per group). On the final day of stress, females were exposed to foreign pups (2 pups; 2 days old) and their maternal behaviors were recorded for 15 minutes. Thirty minutes after behavior, trunk blood and fresh frozen brain tissue was collected. Brains were sectioned on a cryostat and fluorescence in situ hybridization for corticotropin releasing factor, urocortin-3, and c-fos was performed.

In a second set of experiments, we performed a similar chronic restraint stress paradigm in lactating females. Stress was performed on postpartum days 2–16. These experiments are currently ongoing with a cohort of 5 control and 5 stressed females at the time of abstract submission.

Results: Our results show that chronic stress in naïve females significantly decreases the weight of female mice ($p < 0.0001$) and significantly reduces pup retrieval behavior ($p < 0.006$). In control females, there is a significant negative correlation between parental behavior and c-fos positive CRF ($R = 0.68$) or Ucn3 ($R = 0.51$) positive neurons, and chronic stress disrupts this correlation. Analysis of data collected in the lactating female group is currently ongoing, but we are observing similar trends for weight and retrieval behavior.

Conclusions: Here, we show that chronic restraint stress disrupts maternal behavior in both naive and lactating female mice. We find that neural populations in the paraventricular nucleus of hypothalamus that have been identified to play a role in both social and stress-related behaviors, the corticotropin releasing factor and urocortin-3 expressing neurons, are active in females showing less maternal behavior. However, this correlation of activity to maternal behavior is lost after chronic stress, suggesting that stress causes changes in these neurons that disrupts their normal function in maternal behavior and may in part contribute to the observed impact of stress on pup-directed behavior.

Keywords: Corticotropin-Releasing Factor (CRF), Circuitry-Based Approach, Chronic Stress, Hypothalamus

Disclosure: Nothing to disclose.

T18. Transcriptional Profiles in Mouse Models of Treatment Resistant Depression

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Background: Major Depressive Disorder (MDD) is the most prevalent psychiatric disorder worldwide, representing a high level of global economic burden. Despite decades of research, the treatments for MDD remain inadequate for roughly half of patients. Fluoxetine (FLX), a selective serotonin reuptake inhibitor (SSRI), has been widely used to treat MDD, nonetheless, a majority of patients do not achieve full remission. Further, a subset of those afflicted is considered non-responsive to any orally-available treatments, which is termed treatment-resistant depression (TRD). Ketamine (KET), an antagonist of the glutamate N-methyl-D-aspartate (NMDA) receptor among several other actions, has been shown to induce a rapid antidepressant response in ~50% of TRD patients, thus providing a novel therapeutic approach. However, the molecular mechanisms underlying TRD and subsequent response vs. non-response to KET are poorly understood, thus hindering the development of novel treatments. This study was aimed at characterizing the transcriptional profile of successful vs. unsuccessful response to KET in mice that failed to respond to an initial course of FLX as a model of treatment resistance.

Methods: We exposed adult male mice to chronic social defeat stress (CSDS), a validated mouse model for the study of depression that differentiates between resilient and susceptible mouse populations based on the social interaction test (SIT), which is highly correlated with numerous other behavioral outcomes. Mice exhibiting reduced social interaction were classified as susceptible and underwent antidepressant treatment with FLX (160 mg/L/day) in their drinking water for 28 days. A group of susceptible mice received water during the same period (water-treated). After FLX treatment, we identified a subset of mice (~35%) that continued to show reduced social interaction despite treatment (non-responders). FLX non-responders and water-treated mice were subsequently given a single injection of KET (10mg/kg IP) and behavior assessed in the SIT 24 h later. Transcriptome-wide changes in the prefrontal cortex (PFC) and nucleus accumbens (NAc) 48 h after KET administration were profiled by RNA-sequencing.

Results: We found that ~50% of FLX-non-responder mice exhibited an antidepressant response to a single KET injection, a significantly greater response than that seen in susceptible mice treated with water (0%), suggesting that FLX primes mice for successful antidepressant response to KET. We further identified a subset of treatment resistant mice who failed to respond to consecutive FLX and KET treatment. Pattern analysis of the differentially expressed genes in the PFC and NAc revealed transcriptional profiles associated with the antidepressant-like actions of FLX and of KET as well as a series of genes that were unique to treatment resistance to both drugs.

Conclusions: We developed a novel paradigm of treatment resistance in mice that allows for the molecular interrogation of potential mechanisms that underlie antidepressant treatment resistance. The KET response rate in FLX-non-responders is similar to that seen in TRD patients, lending further validity to our model. Moreover, our findings suggest that prior unsuccessful antidepressant treatment induces a "priming effect" that increases the likelihood of successful response to KET. We are now performing weighted gene co-expression network analysis (WGCNA) to identify novel "key driver genes" that may mediate treatment resistance and response across the PFC and NAc, as the encoded proteins could represent targets for the development of novel therapeutics for TRD.

Keywords: Treatment-Resistant Depression, Chronic Social Defeat, RNA Sequencing, Ketamine, Fluoxetine

Disclosure: Nothing to disclose.

T19. Prefrontal Circuit Mechanisms Underlying Stress Effects on Effort-Based Decision Making

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Background: Deficits in effort valuation (EV), a cost-benefit analysis comparing the magnitude of anticipated rewards with effort expenditure required, may contribute to anhedonia in depression, schizophrenia, and other psychiatric conditions. In vulnerable individuals, chronic stress may precipitate anhedonia, which is associated with impairments in reward processing and disrupted EV. Prefrontal cortical are thought to support EV processes, but the underlying mechanisms are not well understood.

Methods: We developed a head-fixed EV task to allow simultaneous 2-photon calcium imaging of dorsomedial prefrontal cortex (dmPFC) neurons through chronically implanted microprisms. We used viral methods to express the genetically encoded calcium indicator, GCaMP7f, in corticostriatal neurons (dmPFC-NAcc) as this population has previously been shown to encode reward-predictive information. Mice (male and female C57/Bl/6, aged 8-12wks) were trained in a classical Pavlovian conditioning task to discriminate between reward-predictive and non-reward-predictive auditory cues. In a later stage of training, "high-effort" trials were introduced, signaled by a tactile cue. Lick responses were continuously monitored and quantified as "anticipatory" or "consummatory" if occurring prior to or following reward delivery, respectively. Following stable EV behavior, male mice underwent chronic social defeat stress (CSDS) for 10 days and were re-tested. Mice were imaged longitudinally across training and following stress exposure. Each cell was tested for low-dimensional encoding of reward- and effort-predictive cues and the accuracy

of cue decoding from population activity was determined by training a linear support vector machine (SVM).

Results: Cue discrimination was validated by an average d-prime value above 0.8. Mice showed sensitivity to reward and effort conditions following learning of the EV task as measured by averaged baseline-subtracted anticipatory and consummatory lick response rates ($N = 15$; $F5,474 = 18.40$; $p < 0.0001$; $F5,489 = 35.60$; $p < 0.0001$). Preliminary neural activity data ($N = 3$; ~500 cells) indicate that ~30% of corticostriatal neurons exhibit statistically significant reward-predictive cue encoding. High-dimensional coding mechanisms were used to examine encoding of reward-predictive cues, as evidenced by accurate cue decoding from population activity (>70%). Stress exposure biased behavioral responding towards low-effort reward-seeking in a subset of mice ($p = 0.008$). CSDS also reduced the accuracy of decoding rewarded trials from corticostriatal population activity, specifically during the reward consumption period.

Conclusions: We are able to use a novel head-fixed effort valuation task to understand how prefrontal projection pathways encode reward- and effort-predictive information for decision making. Additionally, we can examine the effects of psychosocial stress on anticipatory and consummatory reward-seeking behavior, as well as the function of prefrontal circuits. We have found that mice are sensitive to reward value and effort expenditure in our task, and stress-susceptible mice show a selective impairment in high-effort responding following CSDS, and stress may interfere with the encoding of reward-predictive cues by this population of neurons. Ongoing studies are focused on comparing the roles of different PFC projection pathways in reward- and effort-predictive cue encoding and the effect of chronic stress on these circuits.

Keywords: Effort-Based Decision Making Task, Prefrontal Circuit, Calcium Imaging

Disclosure: Nothing to disclose.

T20. The Influence of Working Memory on the Relationship Between Depressive Symptoms and Attention for Dysphoric Stimuli

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Background: Depression is a highly prevalent mental health issue which results in substantial financial burden and life impairment (Greenberg, et al., 2015; Kessler, et al., 2005). Cognitive models of depression suggest that depressed individuals display biased attention for depression-relevant information such as words or images (i.e., dysphoric stimuli) (Beck, 1976; Teasdale, 1988; Ingram, 1984). One factor that contributes to our ability to attend to information is working memory. Research indicates that depressed individuals show deficits in working memory (Rose & Ebmeir, 2006; Moritz et al., 2002). As such, it is possible that working memory deficits may also impact negative attention biases displayed in depressed individuals. However, no studies have directly investigated the relationship between depression symptoms, working memory, and attention to emotional information. This study experimentally examined the role of working memory on the relationship between depressive symptoms and attention for dysphoric stimuli. We tested four hypotheses: 1) increased depression would be associated with increased attention for dysphoric emotional stimuli; 2) increased depression symptoms would be associated with deficits in phonological and visuospatial working memory; 3) there would be an indirect effect of working memory on the relationship between depression symptoms and attention for dysphoric stimuli; and 4) a working memory load would moderate the relationship between depression symptoms and attention for dysphoric stimuli such that under a load condition, the relationship between depressive symptoms and attention for dysphoric stimuli would be stronger than in a no load condition.

Methods: To detect a small to medium effect size (c.f. Armstrong & Olatunji, 2012), we would need to recruit 120 participants to achieve a power of .85. In order to account for eye tracking data loss our sample consisted of 147 participants. After providing informed consent via an IRB approved consent form, participants completed measures of depressive symptoms (PHQ-9), phonological and visuospatial working memory tasks (Rapport et al., 2008), and two runs of an eye tracking task measuring attention bias to emotional facial expressions. During one of the eye tracking runs, participants completed The Serial Three's Task (Smith, 1967) as a working memory load.

Results: Results indicated that increased symptoms of depression were associated with increased attention to dysphoric stimuli ($r = 0.322$, $p = 0.001$). However, depressive symptoms were not associated with deficits in phonological ($r = -0.075$, $p = 464$) nor visuospatial working memory ($r = 0.101$, $p = 0.32$). Furthermore, phonological ($r = -0.017$, $p = 0.871$) and visuospatial ($r = 0.036$, $p = 0.725$) working memory scores were not significantly associated with attention to sad faces. There was not a significant indirect effect of phonological working memory (95% CI = −0.145, .056), nor of visuospatial working memory (95% CI = −0.124, .079) on the relationship between depression symptoms and attention for sad faces. Results indicated a significant interaction between load condition and depression symptoms, $F(1,98) = 9.55$, $p = 0.003$, $\eta p2 = 0.089$. However, this moderation is driven by a significant positive relationship between symptoms of depression and attention to sad faces in the no load condition ($r = 0.322$, $p = 0.001$), but no such relationship in the load condition ($r = -.004$, $p = 0.970$).

Conclusions: Results supported our first hypothesis, but our remaining three hypotheses were unsupported. Limitations of the current study included the use of an undergraduate student sample with depression scores in the mild-clinical range, and the use of a cross-sectional design. It is possible that we did not find a relationship between depression symptoms and phonological and visuospatial working memory because our working memory tasks utilized neutrally-valenced stimuli, whereas some previous research has used negatively-valenced stimuli within their working memory tasks. Additionally, it is possible that the Serial Three's Task was too difficult as a load task, as our data indicated that when under the load condition, participants spent less time looking at almost all emotional faces compared to the no-load condition. Nonetheless, results contribute to the growing literature examining cognitive factors and depression. Future work could examine differing levels of working memory loads, use working memory tasks and a working memory load that are emotionally valenced, or employ a longitudinal design.

Keywords: Cognitive, Depression, Working Memory, Experimental Design, Eye Tracking

Disclosure: Nothing to disclose.

T21. Applying Drift Diffusion Models to Examine the Neural Correlates of Threat Processing in Pediatric Irritability and Anxiety

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Background: Irritability and anxiety are both impairing and often comorbid clinical phenotypes in youth. Behavioral work

has indicated that biased patterns of attention and associated aberrant neural correlates are key pathophysiological mechanisms across both irritability and anxiety (Kircanski et al., 2018). However, progress on understanding the mechanism and tailoring treatment is substantially hindered by limitations in the most widely used method, the dot-probe paradigm, to quantify attention bias. Previous work using drift-diffusion models (DDM) in anxious youth suggests that DDM may be a promising tool to investigate latent mechanisms of attention bias and their association with individual differences. DDM is a well validated computational model which utilizes individuals' distribution of reaction times and response choices across task trials to derive latent metrics indexing cognitive components of task performance. In a dot-paradigm it could derive a more reliable metric indexing biased attention (Price et al., 2018). The present study extends previous work by i) assessing a possible mechanism of attention shifting via the DDM, ii) testing associations between neural activations during the dot-probe show, a latent DDM mechanism, and individual differences in anxiety and irritability.

Methods: A total of 384 participants (ages 8 to 18; M = 12.9 years, 50.3% male) were assessed dimensionally on irritability and anxiety symptoms and completed an fMRI dot-probe task assessing attention bias to angry vs. neutral faces. The DDM parameter of interest was extra-decisional time (t0; task performance components outside of the decision process such as preparation and execution). In the dot-probe paradigm is that threat faces are displayed before the response target appears on the screen which initiates the target-dependent decision process. Hence, orienting to the probe happens before the decision process is initiated (i.e. right-left button press to the direction of the probe). Thus, it is hypothesized that the extra-decisional component contains the process of interest: the time individuals take to orient attention to the location of the probe.

A bifactor model, a data-driven phenotyping approach, was used to identify factors representing shared and unique aspects of anxiety and irritability (Kircanski et al., 2018; Cardinale et al., 2019). Analyses examined the association between clinical phenotype factor scores, DDMt0, and neural activation, as a function of attention orienting to threat.

Results: Extra-decisional time related to attention bias measured by the conventional subtraction score ($r = 0.35$, $p < 0.05$).

We replicated a 4-factor bifactor solution (CFI = 0.954, RMSEA = 0.074 [CI = 0.067, .081]) including three unique factors of irritability and anxiety, and a common factor, termed "negative affectivity", which represents the shared variance of irritability and anxiety. Negative affectivity was associated with increased extra-decisional time across all task conditions (rs = 0.2, $p < 0.05$) and decreased activation in several prefrontal areas (e.g., left and right superior frontal gyrus, $p < 0.005$, whole-brain corrected, cluster corrected to $p < 0.05$) in the attention bias contrast. Neither irritability nor anxiety was associated with extra-decisional time.

During fMRI, increased irritability was associated with widespread increased activation patterns in prefrontal regions (e.g., left medial frontal gyrus, right and left insula, voxelwise $p < 0.005$, whole-brain, cluster corrected to $p < 0.05$). A three-way interaction was found between extra-decisional time and activation to the attention bias contrast as a function of irritability. In youth low on irritability, activation decreased as a function of increasing extra-decisional time in the right superior frontal gyrus ($p < 0.005$, whole-brain corrected, cluster corrected to $p < 0.05$).

Conclusions: Findings support the added value of DDM to characterize aberrant attention processing in pediatric psychopathology. The replication of attention effects on extradecision time should prompt further modeling to partition t0 into orienting versus other unrelated processes or to model the attentional effects on decision processing itself (Nishiguchi et al. 2019).

From a clinical perspective, with emerging evidence supporting the promise of Attention Bias Modification Treatment (ABMT) to treat mood. ABMT is a computer-based attention training program which uses the dot probe to train attention. Enhanced understanding of these processes may contribute to the efforts in tailoring current interventions across different diagnosis.

Keywords: Functional MRI (fMRI), Affective Disorders, Computational Modeling

Disclosure: Nothing to disclose.

T22. Distinctive Learning Styles During Cognitive Training Against Threat Interpretations

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Background: People with affective psychopathology exhibit biased categorical interpretations of ambiguous social information in a manner consistent with their predominant affect. For example, individuals with a tendency towards anger/irritability or anxiety are more likely to label ambiguous facial expressions as threatening, e.g. angry as opposed to happy. These biases may perpetuate pathology-congruent negative cognitions or social interactions. Interpretation bias training (IBT), has been developed to counteract this bias by encouraging more positive judgments of ambiguous social stimuli through reinforcement learning. IBT clinical trials have had mixed outcomes, resulting in prominent calls to understand its mechanism.

One form of IBT is particularly amendable to computational modeling because it requires forced positive/negative judgments of facial affect stimuli with overlapping features. A prominent computational model of categorical learning, ALCOVE (Kruschke, 1992), accounts for such similarity and provides a measure of the speed of learning (learning rate parameter) and the degree to which learning affects similar stimuli (generalization parameter). As opposed to conventional statistics, we expect these parameters to reveal individual differences in trial-by-trial process of learning.

We expected to successfully translate ALCOVE to measure categorical learning during IBT in a transdiagnostic pediatric sample of youth with pathologic anger/irritability and anxiety. We also expected that inter-individual differences in both generalization and learning rate would identify a learning typology.

Methods: Participants were 71 youth (8–22 years old) with no major psychopathology, psychopathology characterized by irritability (Disruptive Mood Dysregulation Disorder), anxiety (any of Generalized, Social, or Separation Anxiety Disorders), or a relevant comparison condition, Attention Deficit/Hyperactivity Disorder. They completed the Affective Reactivity Index (ARI; Stringaris et al., 2012) to assess levels of irritability and the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1997) to assess levels of anxiety. Arbitrary performance criteria independent of model fit and consistent with clinical trials of IBT (e.g., Stoddard et al., 2016) were applied. This yielded a final sample of $n = 63$ [44% female, M (SD) age = 14.7 (3.2) years].

All participants completed an IBT session (Penton-Voak et al., 2012) which required happy or angry judgments of 15 randomly presented pictures of facial affect ranging on a linear morph continuum from overtly happy to overtly angry. A 45-trial assessment block established the angry response probability for each picture. Six 30-trial blocks used feedback to encourage "happy" judgments for two ambiguous morphs on the angry side

of an individual's indifference point. The task ended with another 45-trial assessment block.

The model is a variant of ALCOVE (Kruschke, 1992) modified for use with the IBT task, accounting for baseline emotion valence representation and errors on labeling overt facial expressions (improved fit confirmed by chi-square testing). Parameters of interest were generalization, σ, and learning rate, ε, the latter transformed by taking its fourth root to improve normality.

Results: In this sample, the model assessed generalization and learning rate well. For learning rate, mean ε^0.25 = 0.31 with bootstrap estimated RMSE = 0.12 and parameter recovery r = 0.66. For generalization, mean σ = 5.50, RMSE = 3.61, and parameter recovery r = 0.83.

Best fit Gaussian mixture modeling empirically classified individuals into three, distinctive learning types (BIC = −292.57, entropy = 0.94, BLRT $p = 0.01$). The types were characterized by very low learning rates ["slow learning", $n = 6$, M(SD) σ = 3.29 (2.29), M(SD) ε^0.25 = 0.0021(0.00086)], high generalization and moderate learning ["broad learning", $n = 16$, M(SD) σ = 12.12 (2.76), M(SD) ε^0.25 = 0.26 (0.085)], and variable learning with lower generalization ["narrow learning", $n = 41$, M(SD) σ = 3.25 (1.94), M(SD) ε^0.25 = 0.37 (0.15)]. Of conventional statistics, only a lack of change in indifference point indicated one class, "slow learning".

In regression adjusting for age and accuracy on labeling overt faces, broad learners had lower irritability than narrow learners (ARI b = −0.56, $p = 0.02$). Generalization had a negative association with irritability (ARI b = −0.80, $p = 0.018$) and positive association with anxiety (SCARED b = 0.13, $p = 0.050$).

Conclusions: We translated a prominent category learning model to IBT to discover three distinctive types of learners during this experimental treatment. All types of learners would have been lumped together in an active training group in past trials. However, only 65% of the sample, narrow learners, learned in a way consistent with the theory IBT mechanism of action. One quarter of the sample responded with global improvements to any feedback, which is consistent with concerns about nonspecific 'demand effects' which may have driven past trial results. A tendency to respond to feedback globally was positively associated with anxiety. These findings have implications for examining the mechanism of IBT, explaining the variation in past clinical trial results, and identifying individuals who might benefit from IBT.

Keywords: Computational Modeling, Face Emotion Processing, Category Learning, Interpretation Bias

Disclosure: Nothing to disclose.

T23. Functional Noncoding Variants From Several Major Depressive Disorder GWAS Loci Alter Retinoic Acid Receptor Family Binding Sites

Abstract not included.

T24. Interleukin-8 in Major Depressive Disorder and Effects of Treatment

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Background: Introduction: The inflammation hypothesis of depression postulates that immune hyperactivation and dysregulated cytokine production are involved in the pathophysiology of depressive illness. MDD has been associated with a pro-inflammatory status. Interleukin 8 (IL-8) is a proinflammatory cytokine but also a chemokine that can mediate the migration of inflammatory cells into inflammatory sites and affect the immune response in the acute inflammatory phase. Higher baseline proinflammatory cytokines (e.g., IL-6 and IL-8) levels and poorer antidepressant responses have been found in MDD and BD, although not all studies agree. Other findings indicate that improvement in symptoms of depression and anxiety after treatment is not associated with changes in inflammatory markers. Liu et al. (2020) summarized IL-8 data from nine studies comprising 397 responders and 311 nonresponders. MDD patients who showed improved treatment response at the endpoint had significantly lower baseline IL-8 levels compared with the nonresponders. With respect to potential effects of antipsychotics on IL-8, reported data suggest that antipsychotic treatments alter the gene expression patterns in adipocytes and prime them for a low-level inflammatory state (Sarvari et al., 2014).

Hypothesis: We hypothesized that in the context of a pro-inflammatory status in depression, IL-8 is elevated in MDD patients at pre-treatment and levels correlate with the intensity of depressive symptomatology. We also hypothesized that with successful treatment of depression, the pro-inflammatory state will subside and therefore IL-8 levels at post treatment should be lower than at baseline. In conjunction with escitalopram, an SSRI, and quetiapine, an anti-psychotic, we predicted that our patients' IL-8 levels would change according to previous studies, with a decrease as a result of escitalopram and a decrease as a result of quetiapine.

Methods: Methods: Data was derived from two studies of MDD patients treated either with escitalopram (20 patients) or quetiapine (18 patients). Quetiapine was used in lower doses than those used to obtain an antipsychotic effect, to confirm the utility of this agent to treat depression and anxiety. The potential antidepressant efficacy is related to the active and biologically active metabolite, norquetiapine, that has been shown to be a reuptake inhibitor of norepinephrine. Patients were 20-65 years old and met DSM-IV criteria for MDD. The diagnosis of MDD was made by psychiatric interview and administration of the MINI. A HAM-D >18 score was an inclusion criterion along with absence of any other illness and no evidence of an inflammatory condition. Treatment lasted for 12 weeks. Inflammation biomarkers were measured in blood at baseline and at week 12. In addition, IL-8 levels were correlated at post-treatment with depression scores and depression sub-scores extracted from the HAM-D.

Results: Results: There was a statistically significant difference ($p = 0.007$) between mean Baseline IL-8 values in the MDD group (Mean ± SEM) (4.02±0.71) and the Healthy Control group (1.86 ±0.34). There was no statistically significant difference between Baseline and Week 12 IL-8 values, in either the combined MDD cohort or individual study cohorts. There was no correlation between IL-8 levels and severity of depression or anxiety, at Baseline or at Week 12. When the Baseline values were split into 'High' and 'Low' groups, no statistically significant correlations emerged between IL-8 levels and any of the variables examined. There was no statistically significant difference between Baseline and Week 12 IL-8 values in either treatment group. Baseline IL-8 values did not predict treatment response.

Conclusions: Conclusions: MDD patients had significantly elevated blood levels of IL-8 at pretreatment, suggesting abnormal expression of inflammatory cytokines in depression in support of the hypothesis that immunological abnormalities are involved in the pathophysiology of depression. The observation that IL-8 values did not return to baseline at week 12, in either treatment group, could be due to the short duration of observation. A longer period of treatment might show normalization of IL-8 levels. Lastly, the data indicate that mood normalization may not be accompanied by concomitant normalization of the pro-inflammatory state and a longer duration of treatment may be required to produce immune system homeostasis.

Keywords: Neuroinflammation, Major Depressive Disorder, Interleukin-8, Escitalopram, Quetiapine

Disclosure: Nothing to disclose.

T25. Neurophysiological Signature of Magnetic Seizure Therapy (MST) in Depression and Schizophrenia: A Preliminary Resting-State Electroencephalography Study

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Background: Magnetic seizure therapy is a novel non-invasive neuromodulation treatment under investigation. The aim of MST is to produce a similar therapeutic seizure as (ECT), but with rapidly alternating magnetic fields. The benefit of using magnetic fields is that the seizure-inducing electric fields are delivered directly to the cortex, instead of the scalp as in ECT, allowing the electric field to be more focal and easier to control. The ability of MST to focus the induced electric fields and thereby, the seizure initiation site, makes targeting seizure therapy to specific brain regions possible. Also, as magnetic fields only reach the surface of the neocortex, the induced electric field does not spread to deeper brain structures, such as the hippocampus, as in ECT. This may help alleviate the ECT-associated cognitive impairments, including anterograde and retrograde amnesia. These cognitive impairments are transient but can persist for up to 6 months or longer and are often the main reason why an individual chooses against ECT. Current evidence points that MST has a superior neurocognitive profile to ECT.

So far, MST has been mainly applied in severe depression, but in two studies, schizophrenia has been targeted. In both disorders, MST has obtained promising clinical outcomes. Importantly, the antidepressant efficacy of MST has been similar as in ECT. In schizophrenia, the efficacy of MST has not yet been directly compared to that of ECT.

Due to the different electric field delivery methods, the induced seizures and how they are associated with clinical outcome are different between ECT and MST. ECT induces a seizure in which first the ictal electroencephalography (EEG) increases in amplitude followed by high amplitude polyspike activity which shortly changes into slow wave activity and finally leads to post-ictal suppression of EEG activity. For good clinical outcome in ECT, a long post-ictal suppression is the best indicator of therapeutic response. In MST, both ictal and post-ictal phases are less evident than in ECT and good clinical outcome is associated with low slow-wave amplitude and short polyspike duration. Also, the recovery and reorientation times after treatment differ, and they have been found to be shorter with MST.

Overall, there is still limited understanding of the mechanisms of action and neurobiological effects of MST as well as which neurobiological markers are most likely to show a response to MST. This greatly limits the possibilities of optimizing the treatment to specific disorders. In this study, our aim was to evaluate the neurophysiological signature of MST and whether this signature is similar in depression and schizophrenia.

Methods: MST was administered to 18 individuals (8 males, 44.8 ± 13.0 years) with major depressive disorder (MDD) and 2 individuals (2 males, 38.5 ± 3.5 years) with schizophrenia in a preliminary sample (ClinicalTrials.gov Identifier: NCT01596608). All 20 participants took part in a 64-channel resting-state EEG measurement before and after a course of MST. MST was applied at 100% of maximum stimulator output. The stimulation frequency was between 25 and 100Hz with the MST coil positioned over frontal or vertex brain regions, until adequate seizure was achieved. Treatments were given until the participant remitted or the maximum number of treatments (24 treatments) was given.

Resting-state EEG assessments were preprocessed according to standard guidelines and artifacts were removed with independent component analysis. The power spectrum for each electrode was calculated and relative power was obtained for 1 to 50Hz. Relative power was calculated as the ratio of the power at each frequency relative to the sum of power across all frequencies. Average MST-induced resting-state EEG power change at each EEG frequency was evaluated with the Wilcoxon signed-rank test.

Results: In comparison to baseline, MST increased delta and theta, and decreased gamma power in both MDD and schizophrenia ($p < 0.05$) over the course of the MST treatment. In MDD, however, the low-frequency increases were largely driven by a subset of individuals and were not shared across all participants. No clear pre-MST EEG power trends existed in MDD responders compared to non-responders. But in the persons with schizophrenia, the responder had a low pre-MST EEG power-level while the non-responder had a high pre-MST EEG power level.

Conclusions: MST is a promising seizure therapy under investigation for the treatment of severe neuropsychiatric disorders, such as MDD and schizophrenia. The neurobiological mechanisms of action and effects of MST, however, remain unknown. In our preliminary study, MST showed a similar neurophysiological signature in both MDD and schizophrenia on a group-level, namely there was an increase of power in the lower EEG frequencies and a decrease in the higher frequencies. Neurophysiological markers for MST responders and non-responders, however, may be different across MDD and schizophrenia.

Keywords: Magnetic Seizure Therapy, Major Depressive Disorder (MDD), Schizophrenia, EEG

Disclosure: Nothing to disclose.

T26. Rapid Antidepressant Effects of Selective Slow Wave Sleep Deprivation in Depressed Adolescents: Preliminary Findings

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Background: There is an urgent need for safe, rapid-acting antidepressant strategies for depressed youth. One night of total or partial sleep deprivation (SD) acutely reverses depression in 50% of depressed adults, but these effects are transient, reversing after the next night of sleep. Two small total SD studies in depressed adolescents report similar response rates and, promisingly, more sustained clinical benefits. Yet, SD is not widely-used in depressed youth, perhaps due to patient reluctance to engage in this intervention. Methodological advances now make it easier to non-invasively reduce specific aspects of sleep abnormal in depression, such as non-rapid eye-movement slow wave sleep (SWS). Among depressed adults, selective slow wave sleep deprivation (SW-SD) had the advantage of improving depression without disrupting sleep duration, but remains untested in youth. Among depressed adolescents (13–18yr), we are conducting a pilot experimental study evaluating the antidepressant effects of SW-SD.

Methods: Five adolescent outpatients in a depressive episode ($N = 5$; Mean Age = 15.75yr; 4 Females) completed 3 consecutive nights of overnight polysomnographic sleep monitoring: Baseline (Night 1), Selective Slow-Wave Sleep Deprivation (SW-SD; Night 2), and Recovery (Night 3). Participants slept undisturbed on Baseline and Recovery nights. On the SW-SD night, acoustic stimulation was used to suppress non-rapid eye movement slow wave sleep

(SWS) in real-time (via the sleep EEG) without impacting habitual sleep duration. Participants and clinical raters were told that participants were allocated to SW-SD or a Sham condition on Night 2; however, all participants received SW-SD on Night 2. Clinician-rated depression severity was rated after each night using a modified Child Depression Rating Scale.

Results: There was a significant quadratic effect of night (Baseline vs. SW-SD vs. Recovery) on SWS percentage ($F1,4 = 24.8$, $p = 0.016$). The percentage time spent in SWS was significantly lower on the night of SW-SD relative to Baseline ($p = 0.049$) and Recovery ($p = 0.002$), but SWS on Baseline and Recovery nights did not differ ($p = 0.827$). SW-SD did not significantly affect sleep duration ($p > 0.1$) or the percentage of rapid-eye movement sleep ($p > 0.1$). There was a significant quadratic effect of night on mood ($F1,4 = 47.6$, $p = 0.006$). Clinician-rated depression severity improved after SW-SD relative to Baseline ($p = 0.046$). However, these effects were not sustained after recovery sleep; depression severity increased at a trend level from SW-SD to Recovery ($p = 0.092$). Depression severity did not differ after Baseline and Recovery nights ($p = 0.924$).

Conclusions: Preliminary findings indicate that SW-SD produces acute, but transient, mood improvement overnight in depressed adolescents. However, akin to traditional sleep deprivation/wake therapy, additional therapeutic strategies may be necessary to sustain the rapid-onset antidepressant effect. Data collection for this study is ongoing. If these initial findings are upheld, they would support further evaluation of SW-SD as a rapid antidepressant strategy in adolescents.

Keywords: Adolescent Depression, Polysomnography, Slow Wave Sleep, Sleep Deprivation

Disclosure: Nothing to disclose.

T27. Inhibitory Control and Childhood Psychopathology: A Latent Variable Approach

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Background: Inhibitory control, the ability to modulate prepotent behavior, is postulated to be a core neurocognitive mechanism underlying mood and anxiety disorders. However, previous studies have found mixed support, partly due to variability in the tasks and behavioral metrics used across studies, decreasing the reliability of findings. The current study addresses prior limitations by utilizing a novel, trifold approach. Specifically, we refine four canonical tasks that collectively assess inhibitory control; leverage confirmatory factor analysis to extract a latent construct of inhibitory control across the tasks; and examine associations of this inhibitory control construct with the unique and shared variances of anxiety and irritability in youth.

Methods: A transdiagnostic sample of 171 youth (M age = 12.79 years, 53% female), including individuals with a primary diagnosis of an anxiety disorder, disruptive mood dysregulation disorder (DMDD), or attention deficit hyperactivity disorder (ADHD), and healthy volunteers, completed four canonical response inhibition tasks: Flanker (Eriksen, 1995), Stop Signal Delay (Logan & Cowan, 1984), Antisaccade (Hallett, 1978), and AX-CPT (Rutschmann et al., 1977). We extracted indices of inhibitory control from each task: the reaction time difference between correct congruent and incongruent flanker trials, the stop signal reaction time (SSRT), percentage of correct antisaccade trials, and % of correct AX trials - % incorrect BX trials from the AX-CPT task. Anxiety and irritability symptoms were assessed using the parent-report Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1997) and Affective Reactivity Index (ARI; Stringaris et al., 2012), respectively.

Results: First, a confirmatory factor analysis with the four task behavior indices loading onto a single latent construct of inhibitory control indicated good model fit (CFI=1.00, TLI=1.06, RMSEA=0.00, CI90=[0-0.10]). Participants' scores on the inhibitory control latent variable were extracted. Second, a confirmatory bifactor model (Cardinale et al., 2019; Kircanski et al., 2018) parsing the unique and shared variances of anxiety and irritability also fit the data well (CFI = 0.963, TLI = 0.955, RMSEA = 0.07 CI90 = [0.06-0.08]). Participants' scores on anxiety-specific, irritability-specific, and general (negative affectivity) latent variables were extracted. Third, associations between the inhibitory control and clinical constructs were tested. Interestingly, higher negative affectivity scores, reflecting the shared variance of anxiety and irritability, were associated with significantly poorer inhibitory control ($r = -0.25$, $p < 0.001$), whereas anxiety- and irritability-specific scores were not. This association between negative affectivity and impaired inhibitory control remained significant even after controlling for co-occurring ADHD symptoms ($r = -0.19$, $p < 0.01$).

Conclusions: These results provide novel, transdiagnostic evidence for inhibitory control deficits underlying the shared symptom feature of anxiety and irritability – negative affectivity. The current study highlights an analytic approach in which latent variable analysis can be leveraged to quantify a 'pure' measure of inhibitory control across a range of tasks that differ in their behavioral goals, response modality, and context, increasing statistical power. Such an approach could allow researchers more broadly to overcome limitations inherent in the use of any one task to assess a construct of interest. Further understanding of alterations in inhibitory control in relation to negative affectivity may inform advances in transdiagnostic treatment for youth.

Keywords: Anxiety, Irritability, Latent Factor Analysis, Inhibitory Control

Disclosure: Nothing to disclose.

T28. Evidence of Mu-Opioid Receptor-Mediated Anxiolytic-Like Effect of Oleanolic Acid Acrylate

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Background: Oleanolic acid acrylate (OAA) obtained by single-step esterification of oleanolic acid (a naturally occurring pentacyclic triterpenoid) demonstrated 5-HT1A mediated antidepressant-like effect and provided an antianxiety-like clue in our previous study. Here, we specifically evaluate the anxiolytic-like effect of OAA and the underlining mechanism of actions.

Methods: Acute oral administration of OAA (5, 10 or 20 mg/kg), buspirone 10 mg/kg or vehicle 10 ml/kg was carried out prior to the exposure of 7-week-old male and female Swiss mice [Weight = 28 ± 3 g; $n = 6$ (3 mice per sex) randomly distributed into five groups] to the 5-min light-dark box (LDB), elevated plus-maze (EPM), and 1-min rotarod tests (8 rpm). The mechanisms underlying OAA effect were evaluated through pharmacological pretreatments of mice with WAY-100635 (5-HT1A receptor antagonist) 0.3 mg/kg, naloxone (nonselective opioid receptor antagonist) 3 mg/kg naloxonazine (mu-opioid receptor antagonist) 10 mg/kg or nor-binaltorphimine (kappa opioid receptor antagonist) 10 mg/kg and competitive radioligand binding assays. All experimental procedures strictly adhere to the NIH Guidelines for the Care and Use of Laboratory Animals as approved by the Ethics Committee of the Federal University of Goiás (protocol number 104/08). One- or two-way ANOVA followed by Dunnett´ s

or Bonferroni's post hoc tests, respectively, were used for multiple comparisons of treatment groups. Data are expressed as mean ± SEM with a statistical significance of $p < 0.05$.

Results: The oral administration of OAA (10 and 20 mg/kg) and buspirone 10 mg/kg increased the number of transitions [F (4, 25) = 14.3, $p < 0.05$], and time spent in the light area of the LDB [F (4, 25) = 15.6, $p < 0.05$], as well as the number of open arm entries [F (4, 25) = 4.9, $p < 0.05$] and time spent on the open arms [F (4, 25) = 13.5, $p < 0.05$] of EPM, thereby suggesting a reduction in anxiogenic-like behavior. Non-significant alteration in the first fall latency [F (4, 25) = 0.1, $p < 0.05$] and number of falls [F (4, 25) = 1.1, $p < 0.05$] in the rotarod exclude possible interference of motor performance in this anxiolytic-like response. The involvement of mu-opioid receptor in these activities was shown by the attenuation of the anxiolytic-like property ($p < 0.05$) of OAA 10 mg/kg by only naloxone and naloxonazine pretreatments in addition to the preferential binding affinity of this compound towards mu-opioid receptor (10.3 ± 1.4 nM) as compared to 5-HT1A (58.8 ± 2.2), kappa (595.4 ± 142.3), and delta (Ki > 1000 nM) opioid receptors.

Conclusions: Together, OAA reduced anxiogenic behavioral phenotype and elicited mu-opioid receptor-mediated anxiolytic-like effect.

Keywords: Oleanolic Acid Acrylate, Anxiety Model, Receptor Binding, Mu-Opioid Receptors

Disclosure: Nothing to disclose.

T29. Adult Hippocampal Neurogenesis is Required for Vortioxetine -Induced Prevention of Anxiety/Depression Relapse Phenotype

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Background: Adult hippocampal neurogenesis (AHN) has been implicated in Major Depressive Disorder (MDD) and also in the effects of some antidepressants. Vortioxetine (VORT) treatment, a novel antidepressant which combines serotonin transporter inhibition with actions at serotonin receptors (5-HT1A, 5-HT1B, 5-HT1D, 5-HT3, 5-HT7), was approved by the FDA in 2013 for the treatment of adults with MDD. In a previous study, we showed that after a 3-week withdrawal period VORT treatment protected against stress reinstatement induced anxiety/depression-like phenotype. Interestingly, we also demonstrated that VORT prevented stress -induced decrease in adult hippocampal neurogenesis (AHN). To investigate the potential cellular mechanisms underlying the behavioral effects of vortioxetine, we evaluated whether changes in AHN hypothesized to be relevant for antidepressant action. To this aim, using the glial fibrillary acidic protein (GFAP)-positive neural progenitor cells mouse line, a genetic model for arresting AHN, we examined whether loss of neurogenesis in adult mice altered response and prevention of relapse induced by chronic VORT treatment.

Methods: Four weeks before the start of the corticosterone (CORT) treatment to induced depression-like behavior and until the end of the protocol, male GFAP-TK positive mice (TK+) and their littermates (TK-) were administered with valganciclovir in the chow to arrest AHN. Then, after 4 weeks of chronic vehicle (VEH) or CORT, TK+ and TK- were administered with saline (TK+, $n = 15$; TK−, $n = 16$) or VORT (10 mg/kg/day, i.p, TK+, $n = 15$; TK-, $n = 7$) treatment for 4 weeks. Behavioral assays (Elevated Plus Maze (EPM), the Novelty Suppressed Feeding (NSF), and the Splash Test (ST)) were then chosen to assay anxiolytic- and antidepressant-like activity during VORT treatment and then 3 weeks after withdrawal.

Results: Following determination of an emotionality score, using complementary behavioral analysis of anxiety- and depressive-like behaviors across the EPM, NSF and ST tests, we showed that, chronic VORT induced anxiolytic/antidepressant-like effects ($p < 0.01$) and protected against corticosterone reinstatement –induced anxiety/depression-like phenotype ($p < 0.01$) in both genotype. In the EPM and the ST, ablation of AHN in TK+ mice did not alter both the anxiolytic/antidepressant-like response induced by VORT and prevention of stress reinstatement ($p < 0.01$). However, in the NSF, a neurogenesis-dependent paradigm, chronic VORT treatment induced decrease in latency to feed and prophylactic effects against stress reinstatement in TK- mice, is arrested in TK- mice ($p < 0.01$).

Conclusions: In conclusion, AHN is required not only for VORT -induced antidepressant effects but also for prevention of relapse.

Keywords: Adult Hippocampal Neurogenesis, Antidepressant, Relapse, Depression

Disclosure: Denis J. David: Board Member (Spouse)

T30. Reward Circuit (VTA-NAc) Reactivity During Social Experience, but Not Acute Stress, Predicts Resilience to Chronic Social Defeat Stress in Mice

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Background: Stress can precipitate depression, yet some people are remarkably resilient in the face of adversity. The neural basis of how stress leads to depression and why people are susceptible or resilient remains unknown. The ventral tegmental area (VTA) and nucleus accumbens (NAc) form a circuit in which stress and reward processing converge and this circuit has been implicated in mediating susceptibility and resilience. Here, we tested whether VTA-NAc activity elicited by a brief social experience or stressor predicts susceptibility to chronic social defeat stress (CSDS).

Methods: We recorded local field potential and single unit activity in the VTA and NAc of awake behaving mice as they engaged in Social Interaction and underwent Acute Restraint Stress one day before undergoing ten days of CSDS: For Social Interaction, mice explored a chamber (40 cm x 40.5 cm) containing an empty enclosure for 2.5 min, then explored the same chamber for an additional 2.5 min after we introduced a novel mouse (CD1 male) into the enclosure. For Acute Restraint Stress, mice were securely restrained for 10 minutes using tapered plastic film restraint bags prior to placement in 50 ml plastic conical tubes, modified with breathing holes and a slot along the top to accommodate the chronic electrodes. For CSDS, CD1 retired breeder males (Charles River laboratories) were used as aggressors. For 10 days, we placed the experimental mouse in a different aggressive mouse's homecage for 10 minutes. The mice spent the remaining 24 hours across a perforated, transparent divider from the aggressor. The mice underwent a second Social Interaction test to assess CSDS susceptibility. We analyzed the neural and behavioral data using custom MATLAB scripts.

Results: As expected, CSDS yielded groups of susceptible mice ($N = 11$), who reduced their social interactions, and resilient mice ($N = 6$) who explored at baseline levels. There was no difference between pre-resilient and pre-susceptible mice in the amount of time spent exploring a novel mouse before undergoing CSDS. However, during that social interaction, a lag analysis showed that VTA activity preceded NAc activity in only in pre-resilient mice ($n = 94$ pre-susceptible single units; $n = 40$ pre-resilient single

units; bootstrapping significance testing, $p < 0.05$). Moreover, in pre-resilient mice, NAc single unit firing rates increased with proximity to the novel mouse (Wilcoxon sign rank, $p < 0.001$), while social interaction did not elicit increases in pre-susceptible mice (Wilcoxon sign rank, $p > 0.05$). By contrast, both pre-resilient and pre-susceptible mice had equivalent LFP and single unit responses to acute restraint stress. To ask if these identified group differences in reward circuit physiology could predict, on a mouse by mouse basis who will develop susceptibility or resilience, we used machine learning to develop a linear classifier that predicted resilience with close to 90% accuracy.

Conclusions: These findings lead to the intriguing theory that while both positive stimuli and acute stress impact NAc physiology, resilience develops only due to enhanced baseline neural responses to positive stimuli.

Keywords: Stress Resilience and Susceptibility, Synchrony, Circuit, Machine Learning, Neural Predictors

Disclosure: Genetika+: Advisory Board (Self)

T31. Network-Based Functional Connectivity Predicts Response to Exposure Therapy in Unmedicated Adults With Obsessive-Compulsive Disorder

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Background: Obsessive-Compulsive Disorder (OCD) is associated with alterations in cortico-striato-thalamo-cortical (CSTC) brain networks. Most resting state functional magnetic resonance imaging (rsfMRI) studies of OCD have focused on a priori subcortical (striatal) seeds and reported alterations consistent with the CSTC model. However, more recent whole-brain rsfMRI studies examining functional connectivity across large-scale intrinsic brain networks in unmedicated OCD participants have revealed broader differences in connectivity involving frontoparietal (FPN), default mode (DMN), and salience (also called ventral attention; hereinafter SAL/VAN) brain networks. Such findings suggest OCD pathology may involve an altered functional balance among these networks, wherein the SAL/VAN might fail to appropriately "switch" or modulate between the task-positive FPN and the task-negative DMN. Probing this "triple network" model may expand our understanding of the neurobiology of OCD beyond the CSTC model. Yet, prior studies differ on the direction of relationships among these networks in OCD. To address this conflict in the literature, we used a whole-brain network based statistic (NBS) approach in a sample of unmedicated patients to investigate rsfMRI patterns that differ between adults with OCD and healthy controls and also that predict response to exposure and ritual prevention (EX/RP) psychotherapy in OCD patients.

Methods: Unmedicated adults of both sexes with OCD ($n = 41$) and demographically-matched healthy participants ($n = 36$) completed an MRI scan including two runs of high-resolution multiband rsfMRI (TR = 850 ms, multiband factor = 6, 2 mm isotropic voxels = 7 min and 32 s per run). OCD patients were offered a standardized protocol of twice-weekly EX/RP (17 sessions) administered by a clinical psychologist. Severity of OCD symptoms was assessed pre-, mid-, and post-treatment by a trained rater (independent from the treating clinician) using the Yale–Brown Obsessive Compulsive Scale (Y-BOCS).

Resting state sequences were preprocessed using the Human Connectome Project pipelines v3.4. Nuisance regression (24 head motion parameters, 4 average global grayordinate signal parameters) and motion censoring (frame-wise displacement > 0.25mm, DVARS z-score > 3) were performed. All participants had at least 495 frames (7 minutes) of good data after processing.

The brain was segmented into 352 cortical and subcortical regions using a publicly available CIFTI-space segmentation. Correlations were calculated between each pair of regions and Fisher r-to-z transformed. Analyses examined group differences, including age, sex, and mean framewise displacement (to control for residual effects of participant head motion) as covariates. NBS Connectome was used to implement permutation testing to control for multiple comparisons. Signal extraction using reconstruction independent components analysis (RICA) isolated two independent subcomponents (IC1 and IC2) within the component resulting from NBS.

Analyses examined associations between the ICs and response to treatment in the OCD group. For each IC, a linear mixed-effect (LME) model was conducted in R with Y-BOCS scores as a repeated-measure dependent variable; a random effect for participant; and fixed effects for age, sex, mean framewise displacement, time of assessment, component score for the IC, and the interaction between time and IC score. The IC × time interaction was the predictor of interest, indicating that the slope of change in Y-BOCS scores over treatment differed as a function of baseline resting state functional connectivity.

Results: NBS revealed one component with significantly altered connectivity in patients relative to controls ($p = 0.027$). This component consisted of 23 edges, primarily between regions in the right SAL/VAN and the cingulo-opercular network (CO, highly overlapping with the FPN) and DMN. The right middle and superior temporal gyri formed a hub in this component, with three nodes in these gyri (all mapped to the SAL/VAN) collectively appearing in 21 of the 23 edges. These edges primarily showed reduced connectivity in OCD relative to HC participants with negative connectivity in OCD and near zero connectivity in HC. To characterize these group differences parsimoniously and minimize multiple testing, we used a standard signal extraction method (RICA) to reduce the 23 edges into 2 independent subcomponents.

In the OCD group, LME models tested whether IC1 or IC2 values predicted the slope of change in Y-BOCS scores across EX/RP treatment. Lower (more different from controls) IC2 score significantly predicted greater symptom reduction with EX/RP (Bonferroni-corrected $p = 0.002$).

Conclusions: Using a data-driven, whole-brain approach, we detected altered functional connectivity between regions of the SAL/VAN and the CO and DMN in unmedicated patients with OCD. Moreover, greater magnitude of these alterations predicted greater response to EX/RP. Collectively, these findings support the triple network model of OCD, which proposes that an altered balance between task-positive (ventral attention and cingulo-opercular) and task-negative (default) networks may prevent attending away from intrusive thoughts or urges to perform ritualistic behaviors.

Keywords: Resting-State fMRI, Obsessive-Compulsive Disorder (OCD), Network-Based Statistic (NBS), Salience Network, Ventral Attention Network

Disclosure: Nothing to disclose.

T32. Disruption of Protein Homeostasis as a Pathogenic Mechanism in a Subset of Patients With Schizophrenia

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Background: Despite significant efforts to understand the genetics of schizophrenia, the underlying mechanisms

contributing to the disorder are not well understood and likely to be diverse. Protein aggregation as a pathological process has been implicated in many brain disorders, but its relationship to schizophrenia and other mental disorders is less known. In the present study, we hypothesize that protein aggregation occurs in a subset of patients with schizophrenia and that this pathological process can be identified in human biospecimens.

Methods: Prefrontal cortex or superior temporal gyrus from autopsy brains obtained from the University of Pittsburgh, University of Texas, and Harvard Brain Banks, and olfactory neurons obtained from living subjects from the Johns Hopkins Schizophrenia Center were processed using a fractionation protocol designed to extract the proteins into insoluble and soluble fractions. Levels of protein insolubility and ubiquitin reactivity, markers for protein aggregation, were quantified after SDS-PAGE separation followed by Coomassie staining and Western blot analysis and normalized to total homogenate protein. Mass spectrometry was performed in order to identify the protein composition in the insoluble fraction. Gene Ontology Enrichment Analysis and Ingenuity Pathway Analysis were used to assess the potential biological relevance of the detected proteins in the insoluble fraction.

Results: A subset of patients with schizophrenia showed an increase in markers for protein aggregation, specifically protein insolubility and ubiquitination. Mass spectrometry of the insoluble fraction revealed that cases with increased insolubility and ubiquitination showed similar pattern of peptide clustering by principal component analysis. The proteins that were significantly altered in the insoluble pellet were enriched for processes relating to axon target recognition as well as nervous system development and function. Furthermore, protein insolubility was demonstrated in a subset of patient's olfactory neurons, providing the potential for clinical correlations.

Conclusions: This study demonstrates the pathological process of protein aggregation in a subset of patients with schizophrenia. Understanding the mechanisms related to protein aggregation in schizophrenia could lead to a better understanding of the disease process and novel therapeutic targets.

Keywords: Schizophrenia Subtypes, Schizophrenia (SCZ), Protein Aggregation

Disclosure: Nothing to disclose.

T33. Schizophrenia-Associated Differential DNA Methylation in the Superior Temporal Gyrus is Distributed to Many Sites Across the Genome and Annotated by the Risk Gene MAD1L1

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Background: Many genetic variants and multiple environmental factors increase risk for schizophrenia (SZ). SZ-associated genetic variants and environmental risk factors have been associated with altered DNA methylation (DNAm), the addition of a methyl group to a cytosine in DNA. DNAm changes, acting through effects on gene expression, represent one potential mechanism by which genetic and environmental factors confer risk for SZ and alter neurobiology.

Methods: We investigated the hypothesis that DNAm in superior temporal gyrus (STG) is altered in SZ. We measured genome-wide DNAm in postmortem STG from 44 SZ subjects and 44 non-psychiatric comparison (NPC) subjects using Illumina Infinium MethylationEPIC BeadChip microarrays. We applied tensor composition analysis to extract cell type-specific DNAm signals.

Results: We found that DNAm levels differed between SZ and NPC subjects at 242 sites, and 44 regions containing two or more sites, with a false discovery rate cutoff of $q = 0.1$. We determined differential methylation at nine of the individual sites were driven by neuron-specific DNAm alterations. Glia-specific DNAm alterations drove the differences at two sites. Notably, we identified SZ-associated differential methylation within mitotic arrest deficient 1-like 1 (MAD1L1), a gene strongly associated with SZ through genome- wide association studies.

Conclusions: This study adds to a growing number of studies that implicate DNAm, and epigenetic pathways more generally, in SZ. Our findings suggest differential methylation may contribute to STG dysfunction in SZ. Future studies to identify the mechanisms by which altered DNAm, especially within MAD1L1, contributes to SZ neurobiology are warranted.

Keywords: Epigenetics, DNA Methylation, Postmortem Brain Tissue, Schizophrenia (SCZ), Auditory Cortex

Disclosure: Nothing to disclose.

T34. Enhanced Event-Related Desynchronization of the Alpha Rhythm During a Visual Cortical Plasticity Paradigm in Healthy Individuals and in Patients With Schizophrenia

Abstract not included.

T35. Genetic Variability and Antipsychotic Treatment Effects on Cognitive Performance in Schizophrenia

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Background: The cognitive deficits that accompany schizophrenia are arguably among the most debilitating aspects of the disease. However, antipsychotic treatments have done remarkably little to provide robust amelioration of these severe symptoms. The minimal effects that have been observed in antipsychotic treatment studies often are confounded by flawed designs (e.g., failure to account for practice effects and/or lacking a clear medication-free comparison condition). In order to address some of the limitations inherent in prior studies, we assessed the response to antipsychotic treatment on cognition in individuals with schizophrenia using a comprehensive neuropsychological battery in a dual-armed, blinded, cross-over study comparing monotherapy to placebo treatment. Additionally, we tested how genetic factors may influence medication effects by examining whether polygenic scores for cognitive ability relate to variation in treatment-mediated changes in cognitive performance.

Methods: Seventy-one inpatients (mean age = 29.8 +/− 8.6 years, 23 women) with schizophrenia ($n = 64$) or schizoaffective disorder ($n = 7$) participated in a blinded, cross-over study during which they were carefully observed on the National Institute of Mental Health schizophrenia research ward at the National Institutes of Health Clinical Center. Patients received either antipsychotic treatment monotherapy or placebo for 4-6 weeks and then switched to the alternative treatment condition after a transition period. Near the end of each study arm, patients completed a battery of neuropsychological testing targeting general intelligence, working memory, episodic memory, and verbal fluency. The effects of antipsychotic medication as compared to placebo on performance were examined using separate GLM analyses for each cognitive test. A subset of the study population ($n = 38$) provided blood samples for genotyping. Polygenic scores for cognitive ability (PGScog) for each patient were calculated using summary statistics from a genome-wide association meta-analysis of general cognitive ability (Sniekers et al., 2017). The association between patients' PGScog and their medication-related changes in cognitive performance were

estimated, controlling for ancestry. Additionally, the relationship between change in cognitive performance and chlorpromazine equivalents (CPZE) was also tested. Results with a p value of <0.05, uncorrected for multiple comparisons, for any measure are reported.

Results: Changes in performance between medication conditions were not found for any cognitive measure except for story memory delay, where patients showed worse performance in the off-medication condition ($n = 45$, $F = 7.02$, $p = 0.01$). A post-hoc analysis including only patients who received active medication in the first arm of the study ($n = 25$, $F = 7.29$, $p = 0.01$) bolstered the position that improved story memory performance during active treatment was not due to practice effects. No significant influence of CPZE was observed. Interestingly, genetic predisposition towards greater cognitive ability (PGScog) influenced the effects of antipsychotic treatment on cognitive performance in domain-specific ways: higher PGScog scores were positively correlated with medication-related performance improvements for verbal list learning ($n = 22$, R-squared $= 0.27$, $p = 0.02$) and category fluency ($n = 22$, R-squared $= 0.17$, $p = 0.03$) tasks, but were negatively correlated for the 3-back working memory condition ($n = 38$, R-squared $= 0.07$, $p = 0.04$).

Conclusions: Overall, our results support the idea that antipsychotic medications have limited effects on global cognitive performance, as only the story memory delay condition demonstrated an improvement with treatment. The amount of medications required, as measured by CPZE, did not appear to be a significant determinant of cognitive performance differences between conditions. An individual's genetic background, as measured by PGScog, did relate to performance changes for some measures. These data suggest that genetic variability may offer valuable information when assessing treatment response during development and testing of therapeutics targeted at ameliorating cognitive deficits in the schizophrenia patient population. Understanding an individual patient's genetic background in conjunction with their cognitive and symptom profiles may one day inform which treatment(s) might be beneficial.

Keywords: Cognition, Schizophrenia, Antipsychotics, Polygenic Scores

Disclosure: Nothing to disclose.

T36. The Schizophrenia-Associated Variant in SLC39A8 Alters N-Glycosylation of Critical Proteins in the Mouse Brain

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Background: Multiple glycosylation genes are associated with schizophrenia through GWAS, including a missense mutation (A391T) in the manganese transporter SLC39A8. Many glycosylation enzymes require manganese as a cofactor, and human carriers of A391T have reduced serum manganese, altered plasma glycosylation, and brain MRI changes consistent with altered metal transport. However, the molecular connection between the A391T mutation and schizophrenia risk in the brain remains unknown.

Methods: We investigated brain glycosylation changes in a knock-in mouse model homozygous for the A391T mutation. Different brain regions (cortex, hippocampus, striatum, and cerebellum) from male and female mice ($N > 4$ per group) were analyzed using MALDI-TOF MS glycomics, RNAseq, and glycoproteomics. Statistical analyses between groups was performed using *t*-tests while correcting for multiple comparisons on the transcriptome and proteome level.

Results: Mice homozygous for A391T display several changes in brain glycosylation, with N-linked glycosylation most significantly impaired. RNAseq analysis showed negligible variation, consistent with changes in the activity of glycosylation enzymes rather than gene expression. One third of all detected glycoproteins were differentially N-glycosylated in the cortex, including members of several pathways previously implicated in schizophrenia such as cell adhesion molecules and neurotransmitter receptors.

Conclusions: These findings provide a mechanistic link between the A391T variant and biochemical changes in the brain, furthering our molecular understanding of how this validated risk-allele may contribute to the pathophysiology of schizophrenia. As many glycosylation deficiencies are treated through oral supplementation with enzymatic precursors and cofactors, brain glycosylation changes caused by the A391T mutation may be reversible with manganese supplementation.

Keywords: N-glycosylation, SLC39A8, Schizophrenia (SCZ), Common Variant

Disclosure: Nothing to disclose.

T37. A Systematic Review and Meta-Analysis of Pharmacological Interventions for Reduction of Weight Gain in People With Schizophrenia: 2020 Update

Abstract not included.

T38. The Dorsal Peduncular Cortex is a Cortical Master of Opioid Withdrawal

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Background: The US is in the midst of an opioid abuse and overdose epidemic, with over 115 people dying each day from opioid overdose; this has been declared a public health emergency. Oxycodone is one of the most prescribed analgesics, is the first opioid many people experience, and has physiochemical properties that allow it to accumulate in the brain at rates higher than other opioids, perhaps explaining its considerable abuse potential. In 2018, 1% of people over age 18 reported abusing heroin in the previous 12 months, whereas 6% reported abusing prescription painkillers. Approximately 80% of heroin addicts began by first abusing prescription opioids (SAMHSA). In the past two decades, a great deal of research using animal models drug addiction have focused on a small number of neurobiological systems, most notably the mesocorticolimbic dopamine system, and the corticostriatal glutamate system. While examination of these circuits has been informative regarding the roles of these systems in motivation and reward, it is very likely that understudied brain systems and circuitries play a critical role in driving addictive behaviors.

Methods: We used the iDISCO+ tissue clearing method and light-sheet microscopy to examine whole-brain c-Fos expression in male C57Bl6/J mice following either experimenter-administered saline or oxycodone, as well as following oxycodone self-administration, extinction training, and cue-induced reinstatement ($N = 6$-8/group). The ClearMap Python package was then used to perform automated cell detection, registration to the Allen Brain Atlas, and quantification of cell counts throughout the entire brain. This revealed 39 regions showing significant alterations in c-Fos expression following acute oxycodone injection, and 33 regions with increased c-Fos following cue-induced reinstatement of oxycodone seeking. Of these regions, we chose to further study the dorsal peduncular cortex (DP), a highly understudied structure

that comprises the ventral-most component of the medial prefrontal cortex (mPFC). We have conducted behavioral experiments in male and female C57, Fos-CreERT2, and MOR-Flox mice, including optogenetic and chemogenetic investigation of hedonic responses to oxycodone exposure and dependence. In order to analyze these behaviors, we used the deep-learning based Python library DeepLabCut to perform pose-estimation and behavioral segmentation. To molecularly characterize the DP, we used single-nuclei sequencing and qPCR. We electrophysiologically characterized the DP in male MOR-mCherry mice. Finally, to characterize direct monosynaptic projections from the DP, we used Fos-CreERT2 mice to fluorescently 'tag' the efferent projections of the oxycodone-responsive with an AAV expressing the anterograde tracer Synaptophysin-mRuby. High-throughput analysis of outputs from the DP was then performed using iDISCO+, light-sheet microscopy, and the Ilastik machine learning classifier was used to quantify axons and synapses throughout the brain.

Results: Optogenetic stimulation of ChR2 in the DP produced a real-time place aversion, and this aversion was blocked by prior administration of oxycodone. In oxycodone-dependent mice, ChR2 stimulation of the DP disrupted behavioral responses to oxycodone injection, and exacerbated naloxone-precipitated withdrawal. Contrarily, chemogenetic inhibition of the DP blocks the motivational symptoms of naloxone-precipitated withdrawal. qPCR analysis of Oprm1 expression showed ~2.5-fold enrichment in the DP compared to the neighboring infralimbic cortex, and single-nuclei RNA sequencing shows that Oprm1 expression in DP neurons is highly overlapping with markers of glutamatergic neurotransmission, contradicting the canonical belief that opioids primarily act on GABAergic interneurons in the cerebral cortex. Furthermore, electrophysiological characterization of MOR(+) neurons showed that they have relatively depolarized resting membrane potential compared to neighboring MOR(−) neurons, showed enhanced Ih currents, and were hyperpolarized by DAMGO application. High-throughput analysis of outputs of opioid-responsive neurons in the DP of FosTRAP mice show dense projections to hindbrain regions known to regulate pain, stress, autonomic function, and aversion, including the trigeminal nucleus, parabrachial nucleus (PBN), and rostromedial tegmentum. Optogenetic stimulation of DP terminals in the PBN of FosTRAP mice recapitulated the real-time place aversion of somatic DP stimulation, and additional behavioral studies on this projection are ongoing. In MOR-Flox mice injected with AAV-Cre, a dose of oxycodone that is rewarding in control groups results in development of conditioned place aversion, rather than preference, indicating that selectively deleting the μ receptor from the DP is able to reverse the hedonic valence of opioid exposure.

Conclusions: These data thoroughly characterize the DP, a highly novel and unique opioid-responsive cortical region. The DP shows enriched expression of the μ opioid receptor, and selectively deleting this receptor in the DP reverses the hedonic valence of oxycodone, creating aversion rather than reward. Most interestingly, electrophysiological and single-nuclei sequencing data indicate that this receptor is expressed on glutamatergic output neurons, and anatomical tracing experiments show these neurons projecting to hindbrain regions known to be implicated in addiction and stress responses.

Keywords: Opioid Addiction, Prescription Opioids, Opioid Dependence, Pharmacotherapy, Animal Model, Withdrawal

Disclosure: Nothing to disclose.

T39. Withdrawal From Chronic Alcohol Exposure Dysregulates the Cortical Phosphoproteome in Rats

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Background: Protein phosphorylation constitutes one of the most common post-translational modifications in protein biology. The enzymatic addition or subtraction of a phosphate group onto nucleophilic residues (serine, threonine, or tyrosine) alters the structural conformation of molecules, rendering them active, inactive or otherwise modifying their function. Growing evidence suggests that chronic alcohol exposure induces proteome-wide dysregulation in the brain, and here we sought to bring consensus to potential mechanisms that may mobilize these systemic changes. In this regard, protein kinases regulate phosphorylation states, often serving as "molecular switches" that induce a variety of biological responses, such as changes in protein signaling.

Methods: The animal studies were conducted with the approval of the Institutional Animal Care and Use Committee at the Scripps Research Institute and in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. We broadly examined the cortical phosphoproteome of male Long-Evans rats made dependent on alcohol via vapor inhalation procedures consisting of 14 hours of daily alcohol exposure for 8 weeks (average alcohol blood concentration = 169.1± 13.3 mg/dL). A separate group of rats remained naïve to alcohol during this exposure period and served as non-exposed controls. We then dissected the dorsal and ventral regions of the medial prefrontal cortex (mPFC) 14 days into alcohol withdrawal, coinciding with the emergence of alcohol-induced cognitive impairments in our previous assessments. The dual-region dissection allowed us to compare molecular processes of cognitive behaviors thought to be functionally distinct in these brain regions. The mPFC samples were digested into fragment peptides, labeled with isobaric Tandem Mass Tags for quantitation and enriched for phosphorylation. A separate study utilized similar quantitative approaches, but without enrichment strategies to compare molecular processes in total protein levels.

Results: The data revealed the identification of approximately 11,000 phosphopeptides, of which more than half contained quantifiable spectra. The comparison between alcohol-dependent and naïve controls ($n = 12$/group pooled into 3 biological replicates) revealed 187 significant group differences in phosphopeptides collected from the dorsal mPFC ($P < 0.05$). A kinase enrichment analysis revealed 6 phosphosites in the dorsal mPFC that were associated with changes in synaptic plasticity ($P < 0.01$). Site modification of the glutamate receptor, N-methyl D-aspartate 2B, in the serine-1303 position indicates possible interactions with calcium/calmodulin-dependent protein kinase II (CaMK2), and this phosphosite was upregulated 1.3 fold in dependent rats. In addition, the phospho-motif for CaMK2 (RXXS*) was enriched 2.6-fold (77 matches) over background in a consensus sequence analysis. Preliminary analyses of the dorsal and ventral mPFC proteome demonstrate a commonly upregulated kinase, adenylate kinase 1, that was enhanced 2.1-fold in dependent rats. A neuropathic role for this kinase involved in the hyperphosphorylation of Tau proteins suggests that chronic alcohol exposure may result in the induction of molecular signaling networks associated with neurodegenerative disorders.

Conclusions: These findings suggest that the mechanisms regulating phosphorylation states are dysregulated in alcohol dependence and may contribute to hyperphosphorylated tone in the mPFC during a period of increased susceptibility to alcohol relapse. Follow-up work is exploring the functional relevance of these target kinases against the cognitive-impairing effects of alcohol withdrawal.

Keywords: Phosphoproteomics, Kinases, Alcohol Withdrawal

Disclosure: Nothing to disclose.

T40. Shank3-Mediated Glutamatergic Synaptic Function was Altered in the Prefrontal Cortex After Heroin Abstinence

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Background: Drug addiction is defined as a chronic and relapsing disease, which is characterized by compulsive drug seeking and episodes of relapse despite prolonged periods of abstinence from the drug. Addiction is associated with neuroplasticity in the corticostriatal brain circuitry. The malfunction of glutamatergic projecting neurons from the prefrontal cortex (PFC) to subcortical regions (such as nucleus accumbens and ventral tegmental area) could constitute the pathological impairments in the ability to control drug-seeking behavior. However, the molecular mechanisms for the heroin abstinence-induced neurobiological adaptations in the PFC are still unclear. Evidences have shown that activation of glutamatergic system attenuates the heroin-seeking behavior. To understand the glutamate receptor-involved mechanisms for heroin addiction, we measured genes expression of glutamate receptor subunits Grin1, Grin2a, Grin2b, Gria1 and Gria2, as well as the scaffolding protein Shank3 (that modulates the glutamate receptor homeostasis) in the prelimbic cortex after abstinence from heroin self-administration (SA). In addition, we also assessed glutamatergic synaptic function by measuring the NMDA receptor-mediated synaptic currents in the layer V projecting neurons after heroin abstinence.

Methods: Mice underwent 10 days of saline or heroin SA (50 ug/kg/infusion, 2 h/session). 14 days after the last SA session, animals were sacrificed for the determination of gene expression by real-time PCR and NMDAR-mediated excitatory post-synaptic currents (EPSC) by electrophysiology in the prelimbic area of PFC. We found that Shank3 gene was altered after heroin abstinence. To examine whether Shank3 plays a role in heroin-related behavioral effects, we assessed heroin sensitization (1.25 mg/kg, s.c., 10 days) in Shank3-deficient mice (C-terminal deletion, Shank3+/ΔC). Locomotion was recorded for 1 h every other day; 14 days after the last injection, mice were given a heroin challenge test (1.25 mg/kg) and locomotion was recorded for 1 h. Statistical significance was determined by *t*-test or ANOVA followed by post hoc Bonferroni test.

Results: Mice from heroin SA group had significant more active responses (N = 8-9/group, $F(1,15) = 4.712$, $P < 0.0001$, two-way rmANOVA) and infusions ($F(1,15) = 14.3$, $P = 0.0018$, two-way ANOVA) than saline group. Moreover, Shank3 mRNA level was significantly lower in the prelimbic cortex of animals that underwent 14-day abstinence from heroin SA, comparing to saline controls (N = 4/group, $t(6) = 3.3$, $P < 0.01$, *t*-test). In the meantime, the transcriptions of glutamate receptor subunits were intact. Additionally, comparing to saline group, NMDAR-EPSC amplitudes were diminished after heroin abstinence ($N = 8$ cells from 3 mice/group, $t(14) = 2.529$, $P = 0.0241$, *t*-test), which is associated with decreased Shank3 gene expression. Furthermore, we found that Shank3+/ΔC mice, which have diminished NMDA-EPSC amplitudes in the PFC, had significantly higher locomotor activity than wild-type (WT) mice (N = 6-7/group, $F(5,55) = 4.0$, $P < 0.01$, two-way rmANOVA). During the heroin challenge test, Shank3+/ΔC mice showed greater total distance travelled than WT mice (N = 6–7/group, $F(17,187) = 4.5$, $P < 0.001$; two-way rmANOVA).

Conclusions: In conclusion, these data suggest that decreased Shank3 in the PFC after abstinence from repeated heroin exposure may contribute to the molecular mechanisms of impaired glutamatergic synaptic function, which results in the vulnerability for later on heroin relapse.

Keywords: Medial Prefrontal Cortex, Heroin, Shank3, NMDA Glutamate Receptors

Disclosure: Nothing to disclose.

T41. Fentanyl Abstinence Causes Neuron Subtype Specific Structural and Molecular Changes in the Nucleus Accumbens

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Background: Opioid abuse has risen dramatically over the last decade. Potent, synthetic opioids like fentanyl are responsible for nearly half of opioid-related deaths, yet synthetic opioid abuse remains broadly understudied. Opioids, like other drugs of abuse, engage and alter dopaminergic circuitry to promote continued use and eventual relapse. Neurons in the Nucleus Accumbens (NAc) play a key role in drug abuse and receive dopaminergic input from the midbrain. NAc medium spiny neurons (MSNs) express either dopamine D1 or D2 receptors, and manipulation of their activity can oppositely regulate drug-related behaviors. Drug-related plasticity in NAc is mainly driven by molecular and structural changes to MSNs, but how synthetic opioids alter specific MSN subtypes remains understudied.

Methods: Male and female mice were given fentanyl in the homecage for 5 days (10 μg/mL in drinking water), after which they underwent 10 days of abstinence. We assessed stress-like behaviors with social interaction and elevated plus maze testing in both sexes and assessed increased stress-susceptibility in males with an acute social stressor. To characterize structural plasticity in NAc MSNs, we used a dilute, Cre-dependent eYFP virus to sparsely label D1- and D2-MSNs in D1- and A2A-Cre mice, respectively. To profile molecular changes and identify molecular mechanisms of cell-type specific dendritic remodeling, we used D1- or A2A-Cre mice crossed with RiboTag mice to isolate ribosome-associated mRNA in specific cell types after fentanyl abstinence. We performed RNA sequencing of the D1- and D2-MSN translatome, followed by weighted correlation network analysis (WGCNA). We then further validated genes identified by RNAseq with Nanostring.

Results: Both male and female mice exhibit increased social-withdrawal and stress-like behaviors after fentanyl abstinence. Stress-like behaviors after abstinence were associated with reduced dendritic complexity of NAc D1-, but not D2-MSNs. Using WGCNA, we identified 11 MSN subtype specific gene networks altered by fentanyl abstinence, including a cluster of transcriptionally co-regulated dendritic morphology genes downregulated exclusively in D1-MSNs.

Conclusions: Together, our findings indicate that fentanyl abstinence generates increased stress-like behaviors that are associated with unique structural and molecular changes in NAc D1-MSNs. Our ongoing work aims to test the causal role of our identified gene networks in both behavior and structural adaptations after fentanyl abstinence.

Keywords: Fentanyl, RNAseq, Nucleus Accumbens, Medium Spiny Neurons, Abstinence

Disclosure: Nothing to disclose.

T42. Ibudilast for the Treatment of Alcohol Use Disorder: A Randomized Placebo-Controlled Experimental Study

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Background: Ibudilast, a neuroimmune modulator which non-selectively inhibits phosphodiesterases (PDEs) and macrophage migration inhibitory factor, shows promise as a novel alcohol use disorder (AUD) pharmacotherapy. However, the mechanisms of

action underlying ibudilast's effects on the human brain remain largely unknown. Therefore, the current study explored ibudilast's efficacy of improving drinking outcomes and attenuating neural reward signals in individuals with AUD.

Methods: Fifty non-treatment-seeking men and women with AUD were randomized to receive ibudilast ($n = 23$; 16M/7F; age = 34.13 ± 9.30) or matched placebo ($n = 27$; 17M/10F; age = 31.41 ± 7.75). Participants completed a two-week daily diary study during which they filled out daily reports of their past day drinking, mood, and craving (ClinicalTrials.gov identifier: NCT03489850). Participants completed an fMRI alcohol cue-reactivity paradigm half-way through the study (Day 8). The number of heavy drinking days (HDD; ≥5 drinks/day for males, ≥4 drinks/day for females) were calculated over the study period. A set of generalized estimating equations with compound symmetric structure were run to account for repeated measures of drinking. A general linear model was used to evaluate the effect of medication on alcohol cue-elicited ventral striatal activation, which was selected a priori as the region of interest.

Results: Ibudilast, relative to placebo, reduced HDD across time (OR = 0.55, $p = 0.04$). Ibudilast also attenuated alcohol cue-elicited activation in the ventral striatum compared to placebo ($F(1,44) = 7.36$, $p = 0.01$). Reward-related activation in the ventral striatum predicted subsequent drinking in the ibudilast group ($F(1,40) = 6.85$, $p = 0.01$), such that individuals who had attenuated ventral striatal activation and took ibudilast had the fewest number of drinks per drinking day in the week following the scan.

Conclusions: This is the first study to evaluate the effects of ibudilast, a neuroimmune modulator, on drinking outcomes in a clinical sample with AUD. Together, these findings extend preclinical and human laboratory studies of the utility for treating AUD and suggest a biobehavioral mechanism through which ibudilast acts, namely, by reducing the rewarding response to alcohol in the brain leading to a reduction in drinking. This is a critical proof-of-mechanism whereby modulation of neuroimmune signaling via ibudilast's inhibition of PDEs reduced ventral striatal excitability to salient alcohol cues.

Keywords: Alcohol and Substance Use Disorders, Ibudilast, Neuroimmune Mechanisms, Alcohol Use Disorder - Treatment

Disclosure: Nothing to disclose.

T43. An Integrated Multimodal Model of Alcohol Use Disorder Generated by Data-Driven Causal Discovery Analysis

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Background: Alcohol use disorder (AUD) has a lifetime prevalence of nearly 30%, with 14.4 million adults in the US currently in need of treatment. Despite treatment, 50-80% of individuals relapse within a year. Mechanisms underlying recovery are still not very well understood, specifically how multifactorial causes may be driving this disease. The recent emergence of publicly available large datasets with broad phenotyping and high-quality neuroimaging data allows for a new approach of testing traditional addiction models, which generally propose that the maintenance of addiction can be explained through a handful of mechanisms. Here, we develop a multivariate model of AUD by leveraging a recently developed data-driven machine learning framework to model causal factors underlying AUD.

Methods: In the current study, we leveraged the deep behavioral and psychiatric phenotyping and high-resolution neuroimaging data from the Human Connectome Project (HCP; $N = 926$; 54% male, mean age = 29 yrs; alcohol abuse or dependence: 22%), using AUD symptom count as our primary outcome variable. We selected all available self-report, diagnostic and behavioral measures assessing cognition, emotion, social function, psychiatric dysfunction and personality (100 in total). We applied exploratory factor analysis (EFA) to parse phenotypic measures into a set of underlying constructs, using Monte Carlo permutation analysis to determine statistically significant factors. We analyzed resting-state functional connectivity by parcellating the whole brain data into 718 parcels (Cole-Antecevic parcellation) and then computing within-network connectivity within 12 resting-state large-scale brain networks. We then employed data-driven causal discovery analysis (CDA) to generate an integrated model relating phenotypic factors, functional network connectivity, and AUD symptoms. The particular CDA method we applied, Greedy Fast Causal Inference (GFCI; Ogarrio et al., 2016), uses conditional dependence relations to discover when unmeasured variables confound the relationships between measured variables, making this method particularly powerful for real-world datasets that cannot capture every possible variable of interest. We conducted a stability analysis for the estimated causal graph by resampling 95% of the sample without replacement with 1000 repetitions (jackknifing). Recovered edge weights from Structural Equation Modeling (SEM) were presented overlaid on the GFCI graph.

Results: EFA extracted a set of 18 data-driven factors that represented the wide phenotypic space measured in the HCP dataset. CDA then produced the 30-factor Integrated Multimodal Model of AUD (IMMAUD), which highlighted a multivariate set of causes of AUD, including multiple cognitive, affective, personality, and psychiatric factors, as well as brain network connectivity patterns (12 networks). We found that brain network connectivity measures and phenotypic factors largely separated into two interconnected separate clusters. Brain connectivity intersected with phenotypic variables in a link between fronto-parietal connectivity and fluid cognition. From this point, causal influences propagated from fluid cognition to more specific cognitive measures, including working memory and delay discounting. Lower cognitive scores in turn caused lack-of-agreeableness and lowered social support, which were causally linked to negative affect, internalizing and lack-of-conscientiousness. All of these causes were fully mediated by the sole direct cause of AUD symptoms, externalizing symptoms. A limitation of the used dataset was that approach behavior was not very well characterized, and its role could hence not be described.

Conclusions: Our data-driven model, IMMAUD, provides evidence for a multivariate set of causal pathways underlying AUD. The 30-factor model proposes a hierarchy with causal influence propagating from brain function to cognition to social to affective/psychiatric function and ultimately AUD symptoms. These results underscore that traditional addiction models need to be expanded to highlight the importance of social factors, amongst others. Importantly, the model demonstrated that different pathways exist, which may involve different individuals to different degrees and may hence be targeted separately in personalized treatment approaches. As a consequence, IMMAUD suggests several potential treatment targets for AUD, including neuromodulation of the fronto-parietal network, cognitive/affective interventions, and comorbidity-based interventions.

Keywords: Alcohol Use Disorder, Causal Modeling, Big Data

Disclosure: Nothing to disclose.

T44. Addiction Symptomatology Desensitizes Arousal Response During Impulsive Decision-Making in Opioid Users

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Background: High craving states and increased anxiety are

proximately tied to the decision to seek and consume drugs. In the context of patients with Opioid Use Disorder (OUD) undergoing treatment and intending to reduce their use, this decision implies a risk of relapse, treatment dropout, or even overdose. How can we identify those states in time to act in a preventive manner? Clinical efforts to reduce and prevent relapses are thwarted at least in part by the subjectivity in standard measures used to assess these prodromal symptoms. One alternative is to turn to more objective psychophysiological measures of these states. In this study, we investigate the relationship between a widely used objective measure of arousal (skin conductance response) and impulsive decision-making at different levels of symptom severity in a group of opioid users receiving medication for OUD (MOUD).

Methods: We worked around the methadone schedule of 38 individuals (2 female) under MOUD treatment who endorsed recent craving symptomatology. Participants completed 2 sessions – one before their daily methadone dose and one after (order randomized). In each session, we assessed craving, withdrawal, and anxiety via self-report using validated questionnaires, then asked participants to complete a delay discounting task while skin conductance response (SCR) was measured.

Results: We found SCR to be significantly greater during trials in which subjects made a less as compared to a more impulsive choice in post-methadone ($n = 17$, $p < 0.05$) but not pre-methadone sessions. In post-methadone sessions only, anxiety modulated SCR by increasing it during more impulsive choices and decreasing it during less impulsive choices ($n = 17$, $p < 0.05$). Craving relationship to SCR was differential depending on choice: intensity and episode length were negatively correlated with SCR during impulsive choices (Spearman rho $= -0.626$ and -0.661 respectively, $p < 0.05$, $n = 15$) but positively correlated with SCR during less impulsive choices (Spearman rho=0.777 and 0.759 respectively, $p < 0.05$, $n = 15$). Overall more impulsive individuals showed lower SCR during less impulsive choices (Spearman rho $= -0.719$, $p < 0.05$, $n = 17$).

Conclusions: OUD symptomatology interacts with the relationship between impulsive choice and arousal, desensitizing an individual's arousal response to less impulsive choices when craving and anxiety are high. This result has potentially interesting implications for designing better strategies to aid in detection of symptomatology exacerbation, especially when this may be conducive to more impulsive decisions to resume drug use. Further elucidation of the physiological relationship between craving, anxiety and decision-making could help understand, predict, and prevent relapse in OUD.

Keywords: Delay Discounting, Skin Conductance Response, Opioid addiction, Anxiety, Craving

Disclosure: Nothing to disclose.

T45. Morphine Evokes a Neuroimmune Response in Healthy Volunteers

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Background: There is tremendous need to investigate novel treatment targets for opioid use disorder (OUD), such as the neuroimmune system. In preclinical studies, opioid administration reliably evokes pro-inflammatory responses in the periphery and brain. These pro-inflammatory responses have been shown to influence appetitive (e.g., craving and opioid-seeking) and dysphoric (e.g., pain and withdrawal symptoms) addiction processes and thus, may contribute to the development of OUD and/or perpetuate continued opioid use among OUD patients. In this paradigm development pilot study, we investigated the neuroimmune effects of acute opioid administration using Positron Emission Tomography (PET) imaging with [11C]PBR28, a radiotracer that binds to the 18kDa translocator protein (TSPO), a marker sensitive to immune stimuli. We hypothesized that opioid administration would increase whole-brain TSPO availability and pain tolerance on the Cold Pressor Task.

Methods: Healthy individuals with prior medical opioid exposure ($N = 4$; 3M; 2 'high-affinity' binders; Age=30 years [range = 26–38]; BMI = 26.5 [range = 24–30]) completed two 120-minute [11C]PBR28 PET scans in one day: before and 2-hours after intramuscular morphine administration (0.07mg/kg). Arterial blood was acquired to measure the metabolite-corrected input function. Volumes of distribution (VT), i.e., TSPO availability, were calculated in 10 regions of interest (ROIs) using multilinear analysis–1 (MA-1; t*=30). Regional [11C]PBR28 VT values were evaluated using a repeated-measures analysis of variance with rs6971 genotype as a fixed factor ('high' vs. 'mixed affinity' TSPO binders). Subjective, behavioral, and physiological effects were assayed before and after morphine.

Results: Morphine increased TSPO availability by 28%-39% across ROIs, $F(1,2) = 9.56$, $p = 0.09$, partial $\eta 2 = 0.83$, 'very large' effect. Morphine increased hand withdrawal latency on the Cold Pressor Task, i.e., pain tolerance, $F(1,2) = 3.98$, $p = 0.18$, partial $\eta 2 = 0.66$, 'very large' effect. Morphine decreased systolic and diastolic blood pressure by 11mmHg and 7mmHg, respectively (ps < 0.09).

Conclusions: Preliminary findings for this ongoing pilot study suggest that a side effect of morphine administration is neuroimmune stimulation. If confirmed, this would be the first study to demonstrate a mechanistic relationship between opioid administration and neuroimmune signaling in people, thus providing initial evidence for a plausible role of the neuroimmune system in OUD. The morphine dose administered (<6mg) is comparable to a standard-of-care post-operative analgesic dose. Epidemiological data indicate that 3-10% of healthy individuals treated with opioids for management of surgical pain become long-term opioid users and thus, are high risk for developing OUD. We hypothesize that opioid-induced neuroimmune signaling influences the propensity for long-term opioid use and OUD. The clinical relevance of our findings will be borne out in future studies which will investigate whether pretreatment with a glial modulator, e.g., ibudilast, attenuates morphine's neuroimmune effects and whether supplementing opioids with glial modulators after surgery reduces long-term opioid use (i.e., 'opioid-sparing' effect) and thus, risk for OUD.

Registered Clinical Trial: NCT03801629

Keywords: Neuroimmune Mechanisms, Opioid Side-Effects, Opioid Use Disorder, TSPO and [11C]PBR-28 PET, Pain Analgesia

Disclosure: Nothing to disclose.

T46. Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder: A Randomized Controlled Trial

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Background: Several lines of evidence suggest that classic psychedelics (5-HT2A receptor agonists or partial agonists) such as psilocybin might facilitate behavior change in individuals with substance use disorders.

Methods: We are conducting a multi-site, double-blind, randomized controlled trial to assess the effects of psilocybin-

assisted psychotherapy on alcohol-dependent subjects ($n = 96$). In addition to psychotherapy, participants were randomly assigned to receive psilocybin or diphenhydramine in two dosing sessions separated by four weeks. In the first dosing session, subjects received either 25 mg/70 kg psilocybin or 50 mg diphenhydramine. The dose could be increased to as much as 40 mg/70 kg in the second session, based on response in the first. The duration of treatment in the double-blind period was 12 weeks, followed by longitudinal assessment of drinking outcomes and several potential mediators of treatment effect. The primary outcome measure will be the change in percent heavy drinking days after 36 weeks.

Results: Data collection is ongoing. The study protocol and rationale for design decisions will be presented. We will present baseline data and early results related to the acute effects of psilocybin in study participants.

Conclusions: This is the largest clinical trial in over 30 years to study the therapeutic efficacy of a classic psychedelic. We will report on the safety, tolerability, and acute effects of oral psilocybin in alcohol-dependent participants. This trial lays the groundwork for future studies of the efficacy and mechanisms by which psilocybin-assisted psychotherapy may be clinically useful in the treatment of alcohol use disorder.

Keywords: Psychedelic Medicine, Psilocybin, Alcohol Use Disorder - Treatment, Clinical Trial Design

Disclosure: Nothing to disclose.

T47. Consequences of Escalating Oxycodone Self-Administration on Brain Stress and Reward Function

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Background: Nonmedical opioid abuse is a significant global problem, with an estimated 33 million users of opiates and prescription opioids worldwide. To characterize how prescription opioid abuse develops, this study investigated the affective consequences of escalating prescription opioid use using intracranial self-stimulation (ICSS) reward and oxycodone intravenous self-administration (IVSA) models.

Methods: Male Wistar rats were implanted with chronic indwelling catheters and given access to oxycodone IVSA (0.15 mg/kg/infusion, i.v.) in Short Access (ShA; 1 h) or Long Access (LgA; 12 h) sessions for 5 sessions/week, followed by intermittent 60 h discontinuations from drug access. Another group of rats were prepared with unilateral electrodes aimed at the medial forebrain bundle, trained in the ICSS procedure and then in oxycodone IVSA in 11 h sessions. A separate group of rats were also given LgA access to oxycodone IVSA for 7 sessions/week or pretreated with the kappa opioid receptor antagonist, norbinaltorphamine (norBNI).

Results: Rats given LgA to oxycodone escalated their responding more than ShA rats, with further significant increases ($p < 0.05$) observed following each 60 h discontinuation. Pre-session brain reward thresholds increased with sequential daily LgA IVSA sessions ($p < 0.05$), consequent to successive daily intoxication/abstinence cycles. Manipulation of KOR signaling through daily access or systemic administration of norBNI ameliorated escalation of oxycodone self-administration and changes in brain reward function, whereas infusion of norBNI in the central nucleus of the amygdala resulted in no difference in behavior.

Conclusions: Escalation of oxycodone self-administration is in part due to intermittent abstinence periods and mediated by kappa opioid receptor signaling. These data suggest that timing of medication administration may be a critical factor in setting the stage for oxycodone addiction.

Keywords: Oxycodone, Long Access Self-Administration, Intracranial Self-Stimulation, Kappa Opioid Receptor Antagonist, Rodent Models

Disclosure: Nothing to disclose.

T48. Longitudinal Intravenous Self-Administration in Mice Identifies a Drug Class- and Cell-Type-Specific Role for β-Arrestin2

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Background: A major impediment to the identification of the molecular substrates of addiction and the development of effective therapeutics has been the lack of animal models that both recapitulate the clinical presentation of the disorder and are amenable to genetic engineering. Intravenous (iv) self-administration is considered the gold standard for modeling drug abuse-associated behaviors in animals. However, technical limitations have precluded its wide-spread use in mice: the mammalian species for which the largest numbers of genetics tools are available. Here, we employ an optimized mouse self-administration platform that permits the longitudinal assessment of self-administration acquisition, maintenance, extinction, and cue-induced reinstatement in the same animal. We apply this platform both to the study of cocaine and the short-acting opioid remifentanil. As proof-of-concept, in neuron-subtype-specific knockout mice, we define the role of the G protein-coupled receptor (GPCR) regulatory protein β-arrestin2. β-arrestin2 is a regulator of dopamine receptor signaling, trafficking and desensitization. Critically, β-arrestin2 has been implicated in both human and animal studies of addiction. Expression of the D1R dopamine receptor and the D2R dopamine receptor define two largely mutually exclusive populations of neurons that differentially regulate motivated behavior. The primary objectives of this study were to employ a streamlined approach to the assessment of longitudinal cocaine and remifentanil self-administration in mice and define the role of β-arrestin2 in D1R- and D2R-expressing neurons in these behaviors.

Methods: Longitudinal iv self-administration of cocaine and remifentanil was assessed in mice with selective β-arrestin2 deletion in either D1R-expressing neurons (D1RCre/β-arrestin2f/f, N cocaine/remifentanil = 34/24) or D2R-expressing neurons (D2RCre/β-arrestin2f/f, $N = 26/26$), and in their littermate controls with intact β-arrestin2 expression (WT, $N = 44/36$). Groups were age- and sex-matched. Mice with indwelling jugular catheters were trained to self-administer either cocaine (0.5 mg/kg/infusion) or remifentanil (0.1 mg/kg/infusion) paired with a cue light via lever responding in operant chambers. Mice progressed through 2 lever training and active vs. inactive lever discrimination training at FR1, FR2 and FR4, as dictated by a contingent advancement study protocol. Once acquired, stable active lever responding was assessed at 5 cocaine (0.5, 0.1, 0.3, 1.0 and 3.0 mg/kg/infusion) or 6 remifentanil (0.01, 0.03, 0.1, 0.3, 1, 3 mg/kg/infusion) doses. Dose-response testing was followed by extinction sessions, in which cues were withheld and lever responses had no programmed consequences. After meeting extinction criteria, mice underwent a cue-induced reinstatement session, in which drug-associated cues were presented in the absence of drug reinforcement. Two-way repeated measures ANOVAs were used to assess the effect of FR, drug dose and genotype on individual behaviors. A factor analysis was performed to identify latent constructs contributing to common variance in the datasets.

Results: Cocaine- and remifentanil-associated lever responding was acquired, extinguished, and reinstated in all genotypes. WT mice reached final self-administration acquisition criteria at FR4 in 13.5 ± 3.8 sessions for cocaine and 10.8 ± 1.2 sessions for remifentanil. 84% and 94% of animals with patent catheters acquired the behavior for cocaine and remifentanil, respectively. No significant genotype effects on acquisition were identified, though there was a trend toward increased time to train for the D2RCre/β-arrestin2f/f mice in the cocaine paradigm (16.0 ± 5.6 sessions, $p = 0.0556$). For both drugs, active lever responding was FR and drug-dose dependent. In the cocaine paradigm, D2RCre/β-arrestin2f/f mice self-administered ~30% less cocaine at 0.1, 0.3, and 0.5 mg/kg/infusion doses ($p = 0.0086$) and exhibited increased latency to initiate lever responding ($p = 0.0199$). D2RCre/β-arrestin2f/f mice performed comparably to controls in extinction and reinstatement sessions. D1RCre/β-arrestin2f/f mice could not be discriminated from WT animals at any stage of the cocaine paradigm, and neither D1RCre/β-arrestin2f/f nor D2RCre/β-arrestin2f/f mice segregated from controls at any stage of the remifentanil paradigm. Factor analyses indicated that individual performance in these paradigms was, in part, a function of two latent underlying variables we term incentive motivation (component 1) and discriminative control (component 2). Component 1 scores of D2RCre/β-arrestin2f/f mice in the cocaine paradigm differed from both other genotypes ($p = 0.0011$), suggesting β-arrestin2 deletion in D2R neurons may selectively impair cocaine-associated incentive motivation.

Conclusions: IV self-administration acquisition, maintenance, extinction and cue-induced reinstatement can be systematically assessed using a within-subjects, longitudinal design in genetically modified mice. β-arrestin2 in D2R-expressing neurons regulates self-administration of cocaine but not remifentanil, suggesting that some cellular mechanisms driving reinforcement differ by drug class. The application of this self-administration paradigm to the large and growing number of genetically engineered mouse strains will allow for detailed studies on the contributions of genes to addiction.

Keywords: Drug Addiction, Substance Use Disorders, Intravenous Drug Self-Administration, Cocaine, Opioids

Disclosure: Nothing to disclose.

T49. Pharmacological Determinants of D4R-Selective Antagonist and Partial Agonist Efficacy

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Background: The dopamine D4 receptor (D4R), a G protein-coupled receptor, is predominantly expressed in the prefrontal cortex where it plays important roles in cognition, attention, decision making and executive function. Novel D4R-selective ligands have promise in medications development for neuropsychiatric conditions, including Alzheimer's disease and substance use disorders (SUD). D4R ligands alter cognition and behavior in animal models of drug addiction and variations in the DRD4 gene have been associated with novelty-seeking and risk behavior, as well as ADHD. A better understanding of D4R-mediated signaling is essential to understanding and treating D4R-associated disorders, including SUD. Despite its clinical implications, there are currently few compounds that selectively modulate the D4R receptor. Such compounds are important to study D4R function and identify favorable pharmacology for disease treatment. We created a small next-generation compound library using computational modelling to design D4R ligands based on a 2-(3-(4-(pyrimidin-2-yl)piperazin-1-yl)propyl)benzo[d] thiazole scaffold.

Methods: These novel full- length benzo[d] thiazole derivative ligands were designed using computational modelling. Ligands were synthesized using commercially available intermediates reacted with bis(2-chloroethyl)amine HCl, in diethylene glycol monoethyl ether under reflux conditions, by a nucleophilic substitution reaction with substituted-pyridin-2-amine. Alkylation of the substituted phenyl piperazine moiety with the benzo[d] thiazole compound moiety delivered the target final compounds, which were purified and analytically characterized by CHN combustion analyses performed by Atlantic Microlab, Inc. (Norcross, GA). Compounds in vitro binding affinities were determined using [3H]N-methylspiperone radioligand binding in membranes prepared from HEK293 cells expressing dopamine D2-like receptors (D2R, D3R, or D4R). These binding studies were coupled with functional studies analyzing β-arrestin recruitment and inhibition of cAMP accumulation. We further calculated in silico brain penetration using central nervous system multi-parameter optimization of chemical features (CNS MPO) and also performed Caco-2 membrane permeability tests of selected D4R compounds.

Results: To identify new D4R-selective ligands, and to understand the molecular determinants of antagonist efficacy at D4R, we synthesized and characterized a series of sixteen novel ligands based on the D4R antagonist parent compound. Compounds were profiled using radioligand binding competition assays, β-arrestin recruitment assays, cAMP inhibition assays, and computational modeling. We identified several novel D4R-selective compounds (Ki ≤ 21.2 nM and >100-fold selective vs. other D2-like receptors) with diverse partial agonist and antagonist profiles. Compounds were predicted to be brain penetrant, with calculated CNS MPO scores of ranging 4.5-5.8 for representative compounds (6-point score, with scores > 4 indicating brain penetration). Compounds are expected to be membrane permeable based on the experimental display of the apical-to-basolateral permeability of 27×10^{-6} cm/s for the selected compound CAB-01-019 in the Caco-2 assay.

Conclusions: These compounds highlight receptor-ligand interactions that control efficacy at D2-like receptors. The chemical series includes both partial agonists and antagonists that are selective for D4R with diverse efficacy and are expected to have brain permeation based on parameter calculations and permeability measurements. The results provide further exploration of D4R in drug discovery leading to a better understanding of the role of receptor subtype in neuropsychiatric disorders such as SUD. Future studies will evaluate these analogues in in vivo behavioral studies to provide insight into D4R-targeted drug discovery for SUD, and contribute to the current state of knowledge of D4R functions within the brain.

Keywords: Dopamine D4 Receptor, Antagonist Ligands, Partial Agonist Ligands

Disclosure: Nothing to disclose.

T50. Substantia Nigra Pars Reticulata GABA Neurons: Newly Identified Targets Involved in Heroin Self-Administration and Relapse

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Background: Opioids are highly addictive drugs whose misuse has greatly contributed to the national opioid epidemic. Abuse liability of opioids, including heroin, has traditionally been thought to derive from drug rewarding effects that involve GABA-mediated

disinhibition of dopamine neurons in the ventral tegmental area (VTA). However, this hypothesis has been challenged by recent reports that the rewarding effects of opioids rely on stimulation of mu opioid receptors (MORs) in other brain regions. Notably, the substantia nigra reticulata (SNr), whose native neurons are rich in MORs, has been largely ignored in opioid addiction research. The aim of this study was to dissect the role of SNr GABA neurons in reward and heroin-driven behaviors.

Methods: Using a highly sensitive RNAscope in situ hybridization technique we determined cell-type specific expression of Oprm1 mRNA, encoding MORs, in the midbrain. Next, in a series of experiments with male and female vGAT-cre mice (n = 7–8 per group) and male rats (n = 7–8 per group), we determined the causal role of SNr GABA neurons in opioid addiction using gold standard drug self-administration and relapse paradigms combined with transgenic, optogenetic and intracranial microinjection approaches. The numbers of lever presses during reinstatement were analyzed with (lever x phase x treatment) ANOVAs and infusions with (heroin dose x phase x treatment) ANOVAs.

Results: We found that about 46% of SNr GABA neurons express Oprm1 mRNA, which is in striking contrast to the VTA, where only 28% of GABA neurons express Oprm1 mRNA. Optogenetic inhibition of SNr GABA neurons produced rewarding effects in vGAT-cre mice, as assessed by intracranial self-stimulation (F11, 154 = 2.71; p = 0.003) and real-time place preference (F2, 18 = 7.84, p = 0.004). We also found that in vGAT-cre mice, response-contingent optogenetic stimulation of SNr GABA neurons reduced heroin reward, as evidenced by compensatory increases in heroin self-administration rates (F1, 22 = 9.05; p = 0.006) and attenuated drug-primed reinstatement of heroin seeking (F2,10 = 20.96; p = 0.001), suggesting a critical role for these neurons in opioid reward and relapse. These findings were corroborated by our additional findings that intra-SNr infusions of naloxonazine (a MOR antagonist; 0, 2 or 4 µg/0.5 µl/side) produced similar effects in rats across different doses of heroin (0.0125, 0.025 and 0.05 mg/kg/infusion) (F2, 20 = 6.07; p = 0.009), well beyond those seen with intra-VTA naloxonazine infusions (F2, 21=3.68, p < 0.03). Lastly, intra-SNr infusions of naloxonazine dose dependently reduced heroin-primed (F2, 21 = 9.03; p = 0.01), but not cue-induced reinstatement of heroin seeking in rats, suggesting that SNr GABA neurons play a role in the acute effects of heroin and heroin seeking.

Conclusions: Our findings expand our understanding of the neurobiological mechanisms underlying opioid addiction, pointing to SNr GABA neurons as a key player in some aspects of heroin-related behaviors. While the exact circuitry underlying heroin self-administration and relapse remain to be fully understood, the rewarding effects of heroin that lead to compulsive drug taking and seeking appear to depend on both mesolimbic and nigrostriatal systems. Importantly, our findings also redefine the primary function of the SNr, which has traditionally been thought to be restricted to motor processes and Parkinson's disease, but now can also be considered to play a significant role in opiate reward and seeking

Keywords: Opioid Addiction, Substantia Nigra, Drug Relapse, Mu-Opioid Receptors, Self-Administration

Disclosure: Nothing to disclose.

T51. Circuit-Specific Modulation of Addiction Related Behaviors by Astrocytes

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Background: Traditionally, astrocytes have been considered support cells of the brain. However, although astrocytes are not electrically excitable, astrocytes respond to neurotransmitters with cytoplasmic calcium elevations, which, in turn, can trigger the release of gliotransmitters to modulate synaptic transmission and plasticity. Specifically, astrocytes respond to dopamine and amphetamine with intracellular calcium elevations and mediate the synaptic regulation induced by dopamine and amphetamine in the nucleus accumbens, a major reward center of the brain. The behavioral consequences of astrocyte-mediated amphetamine neuromodulation remain largely unknown. The present study investigates the role of astrocytes in amphetamine-related behaviors and tests the hypothesis that astrocytes modulate behavioral sensitivity to amphetamine.

Methods: Ethics Statement: All animal care procedures were approved by the University of Minnesota Institutional Animal Care and Use Committee (IACUC) with compliance to the National Institutes of Health guidelines for the care and use of laboratory animals. Amphetamine locomotor sensitization: Male and female transgenic mice with deficient astrocyte calcium signaling (IP3R2−/− mice; n = 18; n = 8 males and n = 10 females) and control wild-type background mice (Black Swiss; n = 16; n = 5 males and n = 11 females) were used for behavioral experiments. For saline experiments (IP3R2−/− mice: n = 6; n = 3 males and n = 3 females; Black Swiss mice: n = 6; n = 3 males and n = 3 females). Male and female mice with D1 receptors specifically ablated in astrocytes, GFAP-D1−/− mice (n = 12; n = 6 males and n = 6 females;) and GFAP-D1−/− control littermate mice (n = 11; n = 4 males and n = 7 females) were used for behavioral experiments. For saline experiments: GFAP-D1−/− mice (n = 13; n = 6 males and n = 7 females;) and GFAP-D1−/− control littermate mice (n = 9; n = 4 males and n = 5 females). Mice were ≥ 5 weeks of age. Amphetamine conditioned place preference: Male and female IP3R2−/− mice (n = 12; n = 6 males and n = 6 females), IP3R2−/− control wild-type background mice (Black Swiss; n = 16; n = 5 males and n = 11 females), GFAP-D1−/− mice (n = 24; n = 12 males and n = 12 females;) and GFAP-D1−/− control littermate mice (n = 19; n = 7 males and n = 12 females) were used for behavioral experiments. Mice were ≥ 5 weeks of age. Statistics: Data are expressed as mean ± standard error of the mean (SEM). Data normality was tested using a Kolmogorov-Smirnov test. Results were compared using a two-tailed Student's t-test or ANOVA (α = 0.05).

Results: We found that when compared to wild-type mice, mice with impaired astrocyte calcium signaling (IP3R2-/- mice) demonstrated attenuated behavioral sensitivity to amphetamine (p > 0.001; 2.5 mg/kg, i.p). The extent of sensitization that occurred from day 1 to day 5 was also significantly different between the two groups (p = 0.001). As a control, we investigated the effects of repeated saline injections on locomotor activity and saw no differences between groups or days (p = 0.335). Next, we investigated the role of astrocyte D1-like receptors (D1Rs) on behavioral sensitivity to amphetamine. There was no significant difference in behavioral sensitivity to amphetamine with 2.5 mg/kg i.p. injection in GFAP-D1−/− mice when compared to GFAP-D1WT mice (p = 0.997); however, there was a difference in acute locomotor responsiveness to amphetamine when we increased the dose to 5mg/kg i.p. injection (p = 0.03). We also investigated the contribution of astrocyte calcium signaling and astrocyte D1Rs on amphetamine-induced conditioned place preference. We found that there was no significant difference between IP3R2 −/− mice and wild-type control mice for preference of the amphetamine-paired environment (p = 0.711). Furthermore, we found that GFAP-D1−/− mice and GFAP-D1WT mice demonstrated preference for the amphetamine-paired environment equally (p = 0.896).

Conclusions: In the present study, we utilized two behavioral paradigms to elucidate the role of astrocytes in the behavioral manifestation of the rewarding effects of amphetamine. We found that astrocytes in the nucleus accumbens core preferentially

contribute to the acute psychomotor effects of amphetamine, but not the rewarding effects of amphetamine as measured by conditioned place preference. The study demonstrates that astrocytes specifically contribute to the psychomotor enhancement associated with amphetamine administration, as revealed by attenuated acute locomotor responses to amphetamine in IP3R2-/- mice and GFAP-D1−/− mice when compared to wild-type control mice. However, there was no significant effect of astrocyte calcium manipulation on conditioned place preference. Importantly, locomotor sensitization and conditioned place preference target distinct neural circuits for expression of psychomotor enhancement and place preference. Psychomotor enhancement is associated with innate limbic and movement circuits; whereas place preference involves circuits implicated in learning and memory to associate a specific environment with a drug stimulus, i.e. the hippocampus. The results indicate that astrocytes specifically mediate distinct circuits implicated in drug related behaviors (i.e. locomotor sensitization versus conditioned place preference). Overall, the present study provides evidence that astrocytes contribute to the psychomotor effects of amphetamine and may serve as novel cellular targets for drug addiction therapies.

Keywords: Astrocyte, Mesolimbic Reward Circuitry, Neural Circuit and Animal Behavior

Disclosure: Nothing to disclose.

T52. Potassium Channel Regulation of Divergent Dopaminergic Activity States Impacts Associative Reward Learning

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Background: Associative reward learning is an important and adaptive learning process whereby an organism associates cues with outcomes. Dysfunction in associative reward learning could lead to a number of neuropsychiatric disorders such as substance-use disorder or post-traumatic stress disorder. Understanding the regulators of this learning process could lead to further elucidation of the pathological mechanisms that underlie these disorders. Highly regulated activity states of ventral tegmental area dopamine neurons that maintain intact dopamine signaling in the nucleus accumbens are critical for associative reward learning. A number of intrinsic voltage-gated ion channels are key regulators of these activity states. Here, we sought to elucidate how two voltage-gated potassium channel subunits thought to regulate tonic activity states (Kv4.3) and phasic activity states (KCa1.1) exert their regulatory action on the midbrain dopamine activity to modulate associative reward learning.

Methods: We used a viral-based CRISPR-Cas9 strategy of mutagenesis to target the coding regions of two potassium channel subunits: Kv4.3 (sgKcnd3) and KCa1.1(sgKcnma1) of midbrain dopamine neurons in adult DATiCre mice to create loss-of-function mutations. Next, we performed patch-clamp electrophysiology to confirm functional loss of these ion channel subunits. We then conducted operant conditioning tasks in control, sgKcnd3, and sgKcnma1 mice to determine differences in associative reward learning. Finally, we used fiber photometry to determine alterations to dopamine signaling in the nucleus accumbens.

Results: Using patch clamp electrophysiology, we found that loss-of-function mutations in Kv4.3 (sgKcnd3) increased dopamine neuron firing, suggesting increased tonic activity states, while loss-of-function mutations in KCa1.1 (sgKcnma1) induced an increase in firing irregularity, suggesting increased phasic activity states. To determine if these divergently enhanced activity states differentially impacted associative reward learning, mice underwent operant conditioning (fixed ratio 1 reinforcement followed by extinction). We discovered that sgKcnma1 mice have increased acquisition of the task and slower rates of extinction. However, sgKcnd3 mice have no changes in acquisition of reinforced learning yet higher rates of extinction learning. Fiber photometry recordings revealed distinct alterations to dopamine signaling between these two groups

Conclusions: Here, we profiled how two voltage-gated potassium channel subunits, Kv4.3 and KCa1.1, contribute to dopamine firing and associative reward learning. These models of hyper-tonic and hyper-phasic dopamine activity states can elucidate how disrupted dopamine signaling contributes to dysfunctional associative reward learning.

Keywords: Dopamine, Ventral Tegmental Area (VTA), Associative Learning, Ion Channels, Fiber Photometry

Disclosure: Nothing to disclose.

T53. Reward Filtering Within a Thalamo-Orbitofrontal Circuit Governs Learning Rate

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Background: Many mental illnesses are thought to result from aberrations in associative learning, such as the learning that an environment cue or an action is predictive of an upcoming reward. A simple, yet powerful model for learning that a cue predicts an upcoming reward is to update one's predictions of reward by a reward prediction error (RPE)—the difference between a received and predicted reward. Even though the bulk of experimental work into the neuronal mechanisms of reinforcement learning focus on the mesolimbic dopamine circuitry and its encoding of RPE, a rich computational literature argues that the dopamine RPE circuitry cannot operate in isolation and that the brain likely contains complementary systems for learning. For instance, reinforcement learning algorithms have parameters such as learning rate that also need to be learned within a given environment. A common consequence of such learning is that the learning adapts to the properties and statistics of its environment. Any learning algorithm that optimally adapts to its environment should be capable of identifying when rewards should have low learning rates. For instance, setting the learning rate to be near zero can be highly advantageous to compensate for a slow reduction in RPE as rewards are learned in a static environment, especially when rewards are delayed. Thus, a neural signal that "filters out" a predicted, but delayed, reward will optimize learning. Such a reward filtering system can also optimize learning by filtering out a reward when it is presented with other highly salient stimuli to allocate resources towards the more salient stimuli. It is unknown whether such a reward filtering system exists in the brain. Since prefrontal cortical regions such as the orbitofrontal cortex (OFC) have previously been hypothesized to be involved in representing cognitive variables related to uncertainty in environments, we hypothesized that OFC neurons will show reward filtering to control learning rate of a reward.

Methods: To investigate reward response plasticity in a large number of individual ventral/medial OFC (vmOFC) neurons during reward prediction learning, we used two-photon calcium imaging during a discriminative Pavlovian trace conditioning task in head-fixed mice (Namboodiri et al., 2019). All experiments were approved by institutional IACUC.

This study involved 33 wild type C57/BL6 mice (14 female). Behavioral experiments were conducted under water deprivation, in which animals were maintained at ~85–90% of their pre-deprivation weights. Animals underwent surgery for injection of a virus causing expression of a calcium sensor (AAVDJ-CaMKIIα-GCaMP6s) in vmOFC and in some cases, the injection of AAV5-CaMKIIα-eNpHR3.0-mCherry or the no-opsin control in medial thalamus, so as to study the effect of its inhibition on vmOFC neuronal encoding.

Trace conditioning was done exactly as before (Namboodiri et al., 2019), with an auditory tone (3kHz pulsing tone or 12kHz constant tone, 75–80 dB) lasting 2s paired with a sucrose reward (10–12.5%, ~2.5 µL) 1s after tone offset. This reward paired tone (CS+) was presented randomly interleaved with another tone (12kHz constant tone or 3kHz pulsing tone, 75–80 dB) that did not predict reward (CS−). In another experiment, random unpredictable sucrose drops were delivered along with random unpredictable drops of quinine (1.5–2.5mM) in a 3:1 ratio.

We recorded from a total of more than 7,000 vmOFC neurons across different experiments with and without the inhibition of medial thalamic inputs to vmOFC. These neurons were first clustered based on their responses in trace conditioning to reveal 9 clusters/subpopulations of neurons (Namboodiri et al., 2019). The reward response of these neurons were analyzed across different sessions early in learning, late in learning, a session in which reward probability was reduced to 50%, and a session in which random unpredicted sucrose and quinine were delivered to the animals. Data were analyzed across these conditions using standard statistical approaches.

Results: In this submission, we show using two-photon calcium imaging that some neuronal subpopulations in the vmOFC explicitly signal that a delayed reward is a predicted reward by reversing their reward responses from positive when reward is not predicted (early in learning) to negative when reward is predicted (late in learning) (two-tailed $p < 10^{-9}$ in some subpopulations). Further, since animals typically prioritize punishments/aversive stimuli for learning over rewards, when unpredicted rewards were randomly interleaved with unpredicted presentations of a highly salient aversive stimulus, the same subpopulations again reversed their unpredicted reward responses from positive to negative (two-tailed $p < 10^{-9}$ in some subpopulations). We propose that such reward response plasticity filters out rewards that are less salient for learning. We then show that this activity correlates with behavioral learning rate on a trial-by-trial basis (one-tailed $p < 10^{-16}$ for the whole population). Lastly, we show that medial thalamic inputs to vmOFC exhibit qualitatively similar plasticity as vmOFC neurons, and causally control reward filtering in vmOFC.

Conclusions: In conclusion, we show that vmOFC reward responses control learning rate by filtering out rewards that are less salient for learning. These results open up the possibility that the role of medial thalamus and OFC in mental illness is, at least in part, due to disruptions in setting learning rate.

Keywords: Medial Orbitofrontal Cortex, Orbitofrontal Cortex (OFC), Pavlovian Conditioning, in Vivo Calcium Imaging, Medio-Dorsal Thalamus

Disclosure: Nothing to disclose.

T54. A Dorsal Raphe to Nucleus Accumbens Medial Shell Circuit Underlies Mu-Opioid Receptor Control of Motivation

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Background: Overdose deaths involving opioids have skyrocketed nationally over the last 10 years. Most highly addictive opioids preferentially act on mu opioid receptors (MORs). One major site of MOR action is nucleus accumbens medial shell (NAc). Here, MOR activation has been shown to enhance the motivation for both natural and drug rewards. Despite the powerful effects of MOR activation in NAc on motivated behaviors, the mechanisms underlying their effects are largely unknown. Here, we sought to determine where, when, and how MORs mediate motivated behaviors to better understand how they may become modified in addictive states.

Methods: Male and female adult (8-16 weeks) mice were used for all studies. Behaviorally, mice were tested (8-14/group) on a food intake task in which they were allowed to freely consume sucrose pellets for one hour. Mice were tested while ad libitum or after an acute 24 hour food deprivation. When appropriate, more time-sensitive assays using sucrose pellet dispensers or lickometers were used. Statistically, we used parametric and non-parametric ANOVAs/*t*-tests. Effect sizes and confidence intervals were also calculated to supplement findings. Several mice (3-6/group) were also used for anatomical and electrophysiological experiments.

Results: MOR constitutive knockout ($p < 0.001$) or local microinjections of a MOR antagonist ($p < 0.01$) in NAc reduced food deprived enhancement of intake, but not ad libitum intake. FISH experiments showed that MORs are predominately expressed on medium spiny neurons. We crossed Oprm1fl/fl mice with dynorphin or enkephalin-cre mouse lines to delete receptors from that particular cell type. Loss of MORs on enkephalin ($p < 0.001$), but not dynorphin (n.s.), neurons resulted in decreased hunger-enhanced intake. We also deleted MORs via local or retrograde viral injections in NAc. Only retrograde deletion resulted in reduced hunger-enhanced intake. Retrograde tracing showed labeling in lateral dorsal raphe nucleus. FISH analyses revealed that MORs are expressed on more than 50% of lDRN enkephalin neurons. To test the functionality of this pathway, we injected a MOR rescue virus directly into DRN of MOR knockout x enkephalin-cre mice. This selective rescue of MORs was sufficient to restore hunger-enhanced intake. To further determine whether MORs were specifically acting on DRN-NAc terminals, we injected the calcium indicator GCaMP6s into DRN and placed an optic fiber into NAc to measure changes in fluorescence during food intake. Results show that DRN enkephalin terminals dramatically reduce their activity at the onset of consumption ($p < 0.001$), but only in the food deprived state. This inhibition is blunted by naloxone. To test the functional role of MORs on the terminal, we used the light-activated opto-XR oMOR. Initial tests show that activation of oMOR on DRN-NAc terminals was sufficient to drive intake. Finally, we used of combination of DREADD inhibition ($p < 0.05$), excitation ($p < 0.05$), cell-type specific caspase deletion ($p < 0.001$), and peptidergic deletion of dynorphin (n.s.) or enkephalin ($p < 0.001$) to demonstrate that local enkephalin from NAc D2/enkephalin neurons activate MORs to increase food intake during food deprived states. We additoinally show, using 1-photon in vivo microscopy, that a subgroup of local NAc D2/enkephalin neurons robustly increase their activity just prior to consumption onset.

Conclusions: These results show that MORs in NAc are selectively recruited to enhance motivated behaviors by acting on the terminals of a lDRN projection to NAc shell. Additionally, these terminal MORs are engaged by locally released NAc enkephalin. Future studies could evaluate how this system changes in response to opioid abuse (e.g., fentanyl), or how motivated systems change in response to chronic pain.

Keywords: Nucleus Accumbens Shell, Endogenous Opioids, In Vivo Calcium Imaging, Incentive Motivation

Disclosure: Nothing to disclose.

T55. BNST Intrinsic Connectivity Alterations in Early Abstinence From Alcohol Use Disorder

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Background: The majority of patients in treatment for Alcohol Use Disorder (AUD) will relapse, representing a significant barrier to long-term treatment success. One of the leading triggers of relapse is negative affect, which can persist for months of abstinence. Negative affect during early abstinence is thought to result from neuroadaptative brain changes that occur with chronic alcohol use. Rodent models have identified the bed nucleus of the stria terminalis (BNST) and connected regions (such as the amygdala and anterior insula) as critically involved in negative affect during early abstinence. However, little is known about whether BNST neurocircuitry is altered during early abstinence in humans. The goal of this study is to test the hypothesis that BNST intrinsic connectivity differs during abstinence in individuals with AUD relative to controls. This study represents a critical step in translational research, investigating whether important findings from rodent models translate into humans.

Methods: Twenty individuals with AUD in early abstinence (EA; 9 Female; 30-180 days of sobriety) and twenty healthy controls (HC; 11 Female) participated in the study. fMRI was used to measure BNST connectivity during rest. Intrinsic connectivity was evaluated between the BNST and regions of interest (ROIs) that have previously demonstrated connectivity with the BNST in humans and have been implicated in negative affect: amygdala, anterior hippocampus, anterior insula, hypothalamus, and ventromedial prefrontal cortex. BNST connectivity values were calculated using the Conn Toolbox in SPM12, and average connectivity was computed for each ROI. Group differences were tested using a linear mixed model (lme4) in R with group (EA/HC) and sex (F/M) as fixed factors; hemisphere of the BNST and ROIs were included as covariates. Post-hoc analysis was used to investigate group x sex interactions.

Results: There was a main effect of group for BNST intrinsic connectivity with the hypothalamus (EA < HC; $p = 0.01$) and the anterior insula (EA < HC; $p = 0.006$). For both of these ROIs, HC showed positive connectivity with the BNST, which is not seen in EA. Sex x group interactions were revealed for the amygdala ($p = 0.008$), anterior hippocampus ($p = 0.005$), and hypothalamus ($p < 0.001$). The post-hoc analysis no difference in females (all ps > 0.1), and decreased connectivity in EA males compared to HC males (all ps < 0.005).

Conclusions: Our results indicate that BNST intrinsic connectivity is altered in patients with AUD during abstinence. At rest, healthy controls showed robust intrinsic connectivity between the BNST and the BNST network regions, consistent with previous literature. In the anterior insula and hypothalamus, this connectivity was absent in the EA group, suggesting a critical alteration in this BNST network during early abstinence. In addition, these results differed by sex, with preliminary evidence demonstrating group difference only seen in males. These sex differences are particularly intriguing as there are known sex differences in abstinence symptoms in AUD, with females exhibiting greater levels of negative affect than males. Critical future directions will be to further investigate the role of individual differences in negative affect during abstinence, determine whether BNST intrinsic connectivity changes with longer durations of abstinence, and prospectively assess whether early BNST alterations have a functional impact on risk of relapse. A better understanding of how negative affect and sobriety interact could uncover novel treatment targets for AUD that help patients remain abstinent.

Keywords: Alcohol Use Disorder, BNST, Abstinence, Resting State Intrinsic Connectivity

Disclosure: Nothing to disclose.

T56. Resting State Functional Connectivity Correlates of Rumination and Worry in Internalizing Psychopathologies

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Background: Rumination and worry are transdiagnostic forms of repetitive negative thinking (RNT) that are hypothesized to represent overlapping and unique cognitive processes. Given the role of RNT in the development and maintenance of internalizing disorders, the identification of neural systems supporting these cognitive processes may provide important insights into novel neural targets for intervention. Well-established intrinsic networks (i.e., default mode, salience, executive control, affective) support processes that are hypothesized to underlie RNT. Although emerging evidences suggests involvement of resting-state brain activity in these networks, the majority of research has focused on resting state functional connectivity (rsFC) correlates of rumination within the context of depression. No studies have directly compared rsFC correlates of rumination and worry, and questions remain whether rsFC correlates of RNT are also observed across both depression and anxiety. Therefore, the current study examined relations between rsFC and trait rumination and worry in a transdiagnostic sample of patients with internalizing disorders. We hypothesized that RNT would be associated with rsFC of the default mode, affective, executive, and salience networks. Additionally, we hypothesized that shared and unique correlates of rsFC would be observed for rumination and worry.

Methods: Participants included 80 un-medicated patients (68.8% female, mean age = 26.93 [SD = 7.90]) with a current DSM-5 depression or anxiety disorder. Diagnostic comorbidity was permitted. Resting-state fMRI data was collected, and participants completed trait measures of worry (Penn State Worry Questionnaire; PSWQ) and rumination (Ruminative Response Scale; RRS). Regression analyses, controlling for anxiety and depression symptoms, were performed with seed regions implicated in default mode (i.e., posterior cingulate cortex), executive (i.e., dorsolateral prefrontal cortex [DLPFC]), salience (i.e., dorsal anterior cingulate cortex), and affective (i.e., amygdala) networks. To examine shared rsFC correlates of rumination and worry, both RRS and PSWQ were covariates of interest. To examine unique rsFC correlates of rumination and worry, RRS was a covariate of interest controlling for PSWQ and vice versa.

Results: Whole-brain regression results showed that both rumination and worry were associated with greater positive rsFC between left amygdala and a cluster (k = 572 voxels, z = 4.25, $p < 0.001$) primarily composed of left DLPFC and left inferior frontal gyrus. Conversely, more worry (controlling for rumination) was uniquely associated with greater negative rsFC between right amygdala and a cluster (k = 828 voxels, z = 4.27, $p < 0.001$) primarily composed of bilateral precuneus. No rsFC correlates were uniquely associated with rumination (controlling for worry).

Conclusions: Findings indicated that greater rumination and worry were associated with more positive rsFC between the left amygdala and a cluster of prefrontal regions implicated in the executive control network. Additionally, greater worry was uniquely associated with greater negative rsFC between the right amygdala and a cluster of regions implicated in the default mode

network. Results provide preliminary evidence of shared and distinct rsFC correlates of RNT within the context of internalizing psychopathologies. Findings have potential implications for neuromodulation interventions that target prefrontal neural activity.

Keywords: Resting State Functional Connectivity, Rumination, Worry, Depression and Anxiety, fMRI

Disclosure: Nothing to disclose.

T57. Establishing a Multi-Modal Psychophysiological Profile in Healthy Individuals as a Foundation for Understanding Attentional Preparation and Motivational Processing

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Background: Studies of anticipation that probe reflex reactivity have found sustained startle enhancement during the anticipation of emotional pictures, but increasing inhibition as neutral picture onset nears (Sege et al., 2014). Following anticipation, startle enhancements typically observed during un-cued unpleasant, relative to neutral, picture viewing (Bradley et al., 2001) are reduced or eliminated (Sege et al., 2014; Sege et al., 2015) as a function of predictable cuing. These data demonstrate a pattern of defensive activation in anticipation and subsequent defensive regulation during perception, but not how attenuation coincides with engagement in anticipatory or perceptual processing itself. The current study tested this using event-related potential (ERP), heart rate (HR), and skin conductance (SC) data from our prior investigation (Sege et al., 2014).

Methods: 35 undergraduates (51% male) completed a computer task. On each trial (60 total), a red, blue, or green rectangle was presented for 6 secs, followed by a gray-scale International Affective Picture System (Lang et al., 2008) picture depicting violence, romance, or an everyday event (20 each by color cue) presented for 3 secs, and followed by variable inter-trial intervals (12–21 sec).

EEG data were recorded with a 129 channel Electrical Geodesics system. The stimulus-preceding negativity (SPN), an ERP reflecting preparatory orienting of attention during anticipation, was quantified at frontocentral electrodes from 500–1000 ms post-cue onset. An ERP reflecting picture processing, the late-positive potential (LPP) was quantified at medial posterior electrode sites from 400–800 ms post-picture onset.

HR was recorded from 2 Ag/AgCl electrodes on each forearm, and HR waveforms showed a triphasic response as has been previously observed. Beats-per-minute responses were converted to scores for: Early Deceleration (D1; Minimum HR between 0.5–1.5 sec change from baseline); Acceleration (A; Maximum scores between 3–4 sec deviated from D1); Late Deceleration (D2; Minimum HR deceleration between 5.5–6.5 sec deviated from maximum scores between 3–4 sec). Picture Perception scores also were calculated: Total Deceleration (Minimum HR between 8–9 sec deviated from maximum HR scores between 3–4 sec of the acceleration period); Deceleration from Picture Onset (Minimum HR deceleration 8–9 sec post-cue onset minus the mean HR between 5–6 sec).

SC was collected using 2 Ag/AgCl electrodes on the hypothenar eminence of the non-dominant hand and change scores were calculated by subtracting a mean 1 sec baseline from two Anticipation measurement windows: Early (mean SC 3.5 – 5 sec post-cue onset); Late (mean SC 5.5 – 7 sec post-cue onset). A Picture Perception score also was calculated (mean SC 4 – 5.5 sec post-picture onset minus mean SC 1 – 2 sec pre-picture onset). All measures were analyzed using a repeated-measure ANOVA, and significant effects were followed with pairwise comparisons.

Results: The SPN was modulated by cue, $F(2,31) = 4.10$, $p = 0.03$, $\eta p2 = 0.11$, such that amplitude was more negative for pleasant, $t(32) = -2.60$, $p = 0.01$, $d = 0.45$, and unpleasant, $t(32) = -2.30$, $p = 0.02$, $d = 0.39$, compared to neutral cues, with no difference between pleasant and unpleasant cues. HR D1 was not modulated by cue, nor was the acceleration period (ps > 0.05). D2 was modulated by cue, $F(2,33) = 3.90$, $p = 0.03$, $\eta p2 = 0.10$, showing a larger deceleration for unpleasant, $t(34) = 2.30$, $p = 0.03$, $d = -0.40$, and pleasant, $t(34) = 2.20$, $p = 0.04$, $d = -.40$, compared to neutral cues, but no differences between pleasant and unpleasant cues. SC was not modulated by cue during early or late anticipation (ps > 0.05).

During picture viewing, the LPP was modulated by picture, $F(2,26) = 6.60$, $p = 0.004$, $\eta p2 = 0.20$, showing larger amplitude for unpleasant, $t(27) = 3.40$, $p = 0.002$, $d = -0.53$, and pleasant, $t(27) = 2.80$, $p = 0.001$, $d = -0.64$, compared to neutral pictures, and no differences between unpleasant and pleasant pictures. Total HR Perception Deceleration was modulated by picture, $F(2,33) = 7.40$, $p = 0.002$, $\eta p2 = 0.18$, showing larger deceleration for unpleasant, $t(34) = -3.20$, $p = 0.003$, $d = -0.55$, and pleasant, $t(34) = -3.10$, $p = 0.003$, $d = 0.53$, compared to neutral pictures, and no difference between pleasant and unpleasant pictures. Picture Onset Deceleration was not modulated by picture, $p = 0.37$, but SC showed modulation, $F(2,35) = 4.30$, $p = 0.03$, $\eta p2 = 0.11$, such that there were larger increases for unpleasant compared to neutral, $t(36) = -2.20$, $p = 0.03$, $d = 0.36$, and pleasant, $M = 0.05$; $t(36) = 2.30$, $p = 0.03$, $d = 0.37$, pictures, and no differences between pleasant and neutral pictures.

Conclusions: Results indicate sustained affective reactivity (Sege et al., 2014) coincides with increased preparation of attentional resources during anticipation, and continued enhancements in attentional and general motivational processing during picture viewing despite cuing. Increased SPN and HR deceleration indicate preparatory orienting to anticipated stimuli (Bradley, 2009). Larger LPP amplitudes and HR deceleration during picture perception suggest motivated responding to emotional cued pictures. SC was only enhanced during cued unpleasant picture viewing, however startle reactivity was reduced. These data document typical attentional and emotional response modulation via cuing, which will aid in interpreting cognitive and affective alterations related to psychopathology, and thus, will aid in determining biological mechanisms to target in treatment.

Keywords: Event-Related Potentials, Skin Conductance Response, Emotion Perception, Attention

Disclosure: Nothing to disclose.

T58. Neural Correlates, Psychological and Subjective Effects of Inhaled DMT Experiences: A Field Study in Natural Settings

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Background: Psychedelics are known to strongly modify the conscious experience, making them powerful tools to study the neurobiology of consciousness. Recently, there has been increasing interest in these drugs as treatments for different ailments, mostly in depression and other psychiatric conditions. N,N-Dimethyltryptamine (DMT) presents intense, short-lasting effects, after which subjects return to normal waking state. This tryptamine is found naturally in many plants and animals, and the first records of its use are attributed to Amazonian tribes as part of a brew known as Ayahuasca. There is evidence that a single exposure to this beverage can significantly reduce depression markers for weeks. Few studies to date addressed the neural and

psychological effects of DMT alone, either administered intravenously or inhaled in freebase form, and none conducted in natural settings.

Methods: After a thorough exclusion screening of subjects recruited via social media and word-of-mouth, and screened with a thorough exclusion criteria. We attended inhaled-DMT ceremonies of 35 participants (7 females), in their choice of environment, which provides a familiar and comfortable setting, as opposed to a hospital or laboratory. Combining state-of-the-art wireless electroencephalography (EEG) with psychometric questionnaires we studied the neural correlates, subjective and psychological effects of the experience. Paired *t*-tests were used to compare psychometric (before vs. after) and EEG (DMT vs. baseline) and correlational analyses between EEG features and the scores of questionnaires were performed using Pearson's linear correlation coefficient. We focused on the advantages of conducting field research, including the effects of contextual factors (set and setting), the possibility of studying a comparatively large number of subjects, and the relaxed mental state of participants consuming DMT.

Results: When comparing spectral power of baseline measurements with DMT, we found significant ($p < 0.05$) reductions in the alpha band (8–12 Hz) oscillations throughout all scalp locations, and increases in the delta band (1–4 Hz) and gamma band (30–40 Hz) oscillations. The pharmacokinetics of inhaled DMT was similar to the one reported for intravenous administration, except for a faster return to baseline for power in the alpha band. We were able to quantify and compare the subjective aspects of the experience, and found that 37% of participants presented a complete mystical-type experience. The subjective indicators of these types of experiences correlated positively with gamma power increases ($R = 0.51$, $p < 0.005$). We also found DMT increased global synchrony and metastability in the gamma band, while decreasing both factors in the alpha band. These results are consistent with previous studies of psychedelic action in the human brain, while at the same time suggesting potential EEG markers of mystical-type experiences in natural settings

Conclusions: We conducted one of the first field studies on the neural and psychological effects of a serotonergic psychedelic, yielding new insights and contributing to understanding how much knowledge obtained in laboratory experiments extrapolates to the contexts where these compounds are most frequently consumed.

Keywords: N,N-Dimethyltryptamine (DMT), EEG, Consciousness, Psychological effects, Natural Setting

Disclosure: Nothing to disclose.

T59. Linked Dimensions of Psychopathology and Connectivity in Functional Brain Networks

Abstract not included.

T60. Molecular Characterization of The Stress Network in the Human Brain

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Background: Stress is a major risk factor for the development of a wide range of psychiatric disorders, including schizophrenia and depression. Inter-individual differences in how the brain responds to stress depend on intrinsic (e.g. genetic and developmental) as well as on extrinsic (e.g. hormonal) factors. The neural correlates underlying stress reactivity are currently a growing topic of investigation. Howevr, the molecular mechanisms underlying differences in brain reactivity to stress in humans remain unknown as access to the tissue of interest in humans is limited. Nevertheless, stress-related brain networks as identified by task-based fMRI experiments can be further characterized based on transcriptomic signature by mapping gene expression atlases to identify the molecular mechanisms underlying imaging phenotypes.

Methods: In this study, we examined the putative molecular signatures of brain regions linked to stress reactivity. We linked gene expression data from the Allen Human Brain Atlas (AHBA) to an fMRI-stress networks. We selected brain regions that were differentially affected by stress in individuals with high and low stress sensitivity. Before scanning, participants in the stress groups underwent a Trier Social Stress Test and 30 minutes after the onset of the test, participants performed an emotion-processing task in the magnetic resonance imaging (MRI) scanner based on the International Affective Picture System.

Gene expression data from six healthy brains were acquired from the Allen Human Brain Atlas. In this microarray dataset, probes were mapped to genes as previously described. Z-scores for normalized gene expression levels from the AHBA were calculated separately for each of the six individual brains. Differential expression was determined for the cortical stress network altogether as one mask. We used a bootstrapping approach to assess the robustness of our results with respect to the imbalance between the number of AHBA samples inside and outside the cortical stress network.

To characterize the functionality of the differentially expressed genes, a GO enrichment analysis was performed. Moreover, we assessed whether the differentially expressed genes were enriched for cell type markers, and whether the differentially expressed genes are associated to stress-related psychiatric disorders using a disease-associated gene enrichment analysis was performed based on existing Genome-Wide Association Studies (GWAS) including schizophrenia, bipolar disorder, and major depressive disorder.

Results: Using a meta-analysis approach to combine results across all donors of the AHBA 9 ($n = 6$), we identified 201 differentially expressed genes (BH-adjusted $p < 0.05$). Among those genes, 177 were higher expressed, while the other 24 genes were lower expressed in the cortical stress network compared to the rest of the cortex. Using a bootstrapping approach (see 2.3), we found the identified set of genes to be highly robust to the imbalance between the number of AHBA samples inside and outside the stress network (in 83% of our 1000 iterations, only genes out of our initial 201 differentially expressed gene list were found). The two most differentially expressed genes in the stress-specific cortical regions are Tumor necrosis factor receptor superfamily member 12A (TNFRSF12A) (BH-adjusted p-value = 0.006, log2(FC) = −0.24) and Exosome Component 6 Pseudogene (LOC392145) (BH-adjusted p-value = 0.009, log2(FC) = 0.38).

The differentially expressed genes were enriched for GO terms involved in neuronal development and neurogenesis, synaptic signal transmission, and glutamate receptor signaling. Genes involved in most processes based on GO terms include SHANK, GRIN3A, CNTN4 and ADCYAP1. Enrichment was found for neuronal cell markers (BH-adjusted $p = 5*10-5$), mainly enriched in glutamatergic excitatory neurons compared to GABAergic and non-neuronal cells (p-value = 2.2*10-16). Using GWAS studies, enrichment was found for neuropsychiatric disorders (schizophrenia, bipolar disorder, and autism spectrum disorder) but not for non-brain diseases (e.g. osteoporosis) and non-disease traits (e.g. height and waste-hip-ratio). Differentially expressed genes in brain the stress network were also enriched for DNA-binding loci of that (in the rat) for both the GR and the MR.

Conclusions: We identified genes and pathways in the cortical stress network based on an fMRI-based study involving acute stress exposure. By combining fMRI data to gene expression data, we found 201 differentially expressed genes involved in neuronal

processes and enriched in stress-related psychiatric disorders. Moreover, the enriched genes included several neuropeptides and neurotransmitter receptors with regulation by both the GR and MR and substantial links to HPA-axis activity. This gene set uncovered by combining human gene expression and neuroimaging results give important new insights into the putative neural populations and mechanisms underlying stress vulnerability in humans.

We showed that genes possibly underlying stress reactivity are associated with several neuropeptides and receptors, and this information is not only important to understand the underlying mechanisms of stress vulnerability, but can also be used to develop new drug targets. Therefore, identification of novel drug targets involved in stress vulnerability would be of great interest for the development of new therapies in stress-related psychopathology.

Keywords: Brain Stress, Functional MRI (fMRI), Gene Expression, Stress Reactivity, Stress and Depression

Disclosure: Nothing to disclose.

T61. Latent Variables for Region of Interest Activation During the Monetary Incentive Delay Task

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Background: The Monetary Incentive Delay Task (MID) has been used extensively to probe anticipatory reward processes. However, individual differences during this task may relate to other constructs such as general arousal or valence processing (i.e., anticipation of negative versus positive outcomes). This study used a latent variable approach to parse activation patterns during the MID within a transdiagnostic clinical sample. The current aims were to extend the utility of the MID by: (1) identifying latent variables of regional brain activation during anticipation of reward and loss; and (2) determining if neural factors relate to self-report factors of positive and negative valence. We employed group factor analytic (GFA) approaches among the first 500 participants recruited for the Tulsa-1000 (T1000), a naturalistic longitudinal study of 1000 individuals, including the MID and several relevant self-report measures. Factor analytic techniques offer a novel approach to indexing regional blood oxygenation level-dependent (BOLD) fMRI responses and disentangling factors of neural processing. The current study examined activations corresponding to recent meta-analytic findings of MID anticipation using Brainnetome atlas regions of interest (ROIs). Furthermore, we examined the potential for latent variables to explain variability across brain-derived and self-report variables as well as their relationship to symptoms and/or diagnosis of substance use, depression, and anxiety disorders.

Methods: Participants were drawn from the first 500 individuals recruited for the Tulsa-1000 (T1000), a naturalistic longitudinal study of 1000 people aged 18-55 ($n = 476$ with MID data). We employed group factor analysis to characterize factors within and across variable sets consisting of: (1) region of interest (ROI)-based blood oxygenation level-dependent (BOLD) contrasts during reward and loss anticipation; and (2) self-report measures of positive and negative valence and related constructs. The model included 248 ROI and 13 self-report predictors (subject to predictor ratio of 1.82). Previous simulation research utilizing Bayesian inference to prevent overfitting has demonstrated the adequate performance of GFA in subject to predictor ratios from .04 up to 1.07; thus, the current ratio of 1.8 exceeds this consideration.

Results: Three factors comprised of brain indicators emerged to predict >43% of variance, which had factor loadings suggesting they represent (F1) general arousal or global task activation; (F2) valence, with dissociable responses to anticipation of reward versus loss; and (F3) region-specific activation, with dissociable activation across salience versus perceptual brain networks. Two other factors (F22 & F26) were comprised of self-report variables, which appeared to represent arousal and valence, respectively. Median correlation values of the factors across the 10 replicates conducted in the GFA indicated the robust factors were reliable (all r's > 0.8). ANOVA models indicated that only F22 differed across diagnostic groups, $F(5,460) = 2.35$, $p = 0.0402$. Pairwise comparisons indicated healthy controls had a higher mean score ($M = 0.24$) relative to individuals with major depression ($M = -0.23$; $d = 0.53$, CI95 [0.18-0.89]), indicating higher positive and lower negative affect. It is important to note that the omnibus effect would not survive correction for multiple comparisons. Independent sample *t*-tests indicated that only F2 differed by sex, $t(375.98) = -1.99$, $p = 0.046$, $d = 0.21$, such that males ($M = 0.12$) had higher scores than females ($M = -0.06$), indicating greater differential activation during gain compared to loss anticipation. Regression models indicated that age only predicted F3 ($\beta = 0.11$, $p = 0.015$, $R^2_{adj.} = 0.01$) suggesting older participants demonstrated larger differentiation between subcortical, superior temporal, and cingulate regions as compared to inferior parietal, inferior temporal, middle frontal, and occipital cortical regions.

Conclusions: Results indicate that factor analytic techniques offer a novel approach for differentiating more general arousal or task-based signal and valence-related or region-specific neural activation. These findings are consistent with theoretical assertions that anticipatory affect comprises both arousal and valence. However, these data do not preclude the interpretation that F1 represents a global signal that may not be specific to MID. As such, future GFA work is needed within other fMRI tasks to determine is a similar factor is revealed. Such results would indicate the utility of this method would lie in the ability to distinguish a global signal from task specific effects. Results also indicated that men had higher levels of differential brain activation between anticipation of gains as compared to losses. Furthermore, results indicated that there was a significant association of age and F3, which may reflect differential impacts of age on regional brain volume across the ROIs or distinct patterns of network-based activation during gain and loss anticipation. The size of these effects was small consistent with recent work demonstrating more traditional ROI based analyses conducted in large samples designed to reduce false-positive results. Such factor-analytic approaches may offer insight into neural processing patterns and be useful for probing individual differences and developing better explanatory or predictive frameworks.

Keywords: Monetary Incentive Delay Task, Functional MRI (fMRI), Latent Factor Analysis

Disclosure: Nothing to disclose.

T62. The Atypical Hallucinogen Salvinorin A Alters Activity and Functional Connectivity of the Human Claustrum

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Background: Classic hallucinogens (serotonin 2A receptor, or 5-HT2AR, agonists) and atypical hallucinogens (including kappa-opioid receptor, or KOR, agonists) differ widely in apparent receptor pharmacology, but seem to evoke similar acute subjective effects (MacLean et al. 2013; Maqueda et al. 2015).

Salvinorin A (a selective KOR agonist and atypical hallucinogen with no 5-HT2AR affinity) produces rapid, transient, and profound shifts in subjective experience that are similar to the effects of classic hallucinogens (which do not have affinity for the KOR). The mechanisms through which different classes of hallucinogens with such disparate pharmacology can elicit similar experiences has not been established.

Administration of classic psychedelics leads to glutamate-mediated increases in cortical excitability (Nichols 2016) and acute disruption of task-negative and task-positive cortical networks (e.g. Carhart-Harris et al. 2012, 2016). The claustrum is a thin grey-matter structure nested between the insula and the external capsule that possesses bidirectional glutamatergic connections with the majority of the cortex (Kim et al. 2016) and that has been implicated in supporting cognitive control and the regulation of cortical networks (Krimmel et al. 2019). The claustrum highly expresses receptor targets of both classic and atypical hallucinogens, including 5-HT2AR (Pazos et al., 1985) and KOR (Quirion et al. 1987, Sim-Selley et al. 1999, Ragen et al. 2015), and thus is a potential target for the effects of both classic and atypical hallucinogens. The subjective effects of psilocybin, a classic hallucinogen (and 5-HT2AR agonist), were shown to be associated with the degree to which psilocybin reduced claustrum activity and altered claustrocortical functional connectivity (Barrett et al. 2020). In this preliminary study, we investigate whether salvinorin A also alters claustrum activity and functional connectivity.

Methods: 12 hallucinogen-experienced male volunteers (age: 23-52, M = 36.4, SD = 8.1) completed two single-blind drug administrations, each during separate 20 minute blood-oxygenation level-dependent (BOLD) echo-planar imaging scans (1320 TRs, TR = 907 ms, total acquisition time = 20 minutes, voxel size = 2 mm3, multiband acceleration factor = 6) using a Siemens MRI at 3T with a 32-channel headcoil. The first single-blind drug administration/scan involved inhalation of placebo (hot air) and the second involved inhalation of 15 μg/kg vaporized salvinorin A. One female volunteer qualified and enrolled in the study, but displayed amnesia during a pre-MRI safety session, and was not continued. Preprocessing and analysis of BOLD data followed our previously reported method of small region confound correction to isolate region of interest (ROI) time courses for the left and right claustrum from the surrounding insula and putamen (Krimmel et al. 2019, Barrett et al. 2020). Briefly, BOLD data underwent slice timing correction, realignment, coregistration, normalization to MNI space using unified segmentation, regression of nuisance variables (six motion regressors from realignment, a scrubbing vector, and the first 5 principal components of twice eroded cerebro-spinal fluid and four-eroded white matter masks), detrending, despiking, and band pass filtering [0.008–0.09 Hz]. The average timeseries from each claustrum ROI (left and right) was then regressed on the timeseries of ipsilateral 'flanking' ROIs (insula and putamen), and the residuals from this analysis constituted corrected right and left claustrum corrected time-series. The amplitude of low frequency fluctuations (ALFF) and the variance in the BOLD timecourse of claustrum ROIs were computed as measures of claustrum activity and compared between drug conditions using a Student's T-test. All pairwise correlations between the timecourse of each claustrum ROI and each ROI within the Power atlas (Power et al. 2011) were computed as measures of claustrocortical functional connectivity and compared between drug conditions using mixed-effects general linear models. Claustrocortical connectivity was also correlated with integrity (within-network connectivity) of each cortical network defined in the Power atlas.

Results: Salvinorin A decreased ALFF ($t = 3.32$, $p < 0.001$) and variance ($t = 2.44$, $p < 0.001$) of the right claustrum, and decreased the average connectivity of the right claustrum with regions of the default mode network (DMN) ($F[1,1390] = 65.77$, $p < 0.0001$) and the dorsal somatosensory network ($F[1,718] = 25.5$, $p < 0.0001$). Salvinorin A also increased the average connectivity of the left claustrum with regions of the salience network ($F[1,430] = 10.89$, $p = 0.001$). Right claustrum connectivity with the DMN was associated with the integrity of the DMN ($F[1,1390] = 18.92$, $p < 0.0001$).

Conclusions: Psilocybin was recently shown to decrease claustrum activity and claustrocortical functional connectivity, especially with regions of the DMN, in humans; DMN integrity was associated with right claustrum connectivity with the DMN, and psilocybin subjective effects correlated with the degree of claustrum disruption (Barrett et al. 2020). The current data suggest that atypical hallucinogens such as salvinorin A may also disrupt claustrum activity and connectivity, and subsequently cortical brain network integrity. These findings suggest that claustrum disruption may represent a common mechanism supporting effects of hallucinogens across different drug classes.

Keywords: Claustrum, Psychedelics, fMRI Functional Connectivity, Default Mode Network (DMN), Salvinorin A

Disclosure: Nothing to disclose.

T63. Striatal Low-Threshold Spiking Interneurons Locally Gate Dopamine During Learning

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Background: Low-threshold spiking interneurons (LTSIs) in the dorsomedial striatum (DMS) are potent bidirectional modulators of instrumental learning. While we previously demonstrated that reward-circumscribed LTSI activity causally influences learning, the underlying mechanisms remained unclear. Dopamine (DA) transmission is critical for learning and performance of goal-directed behavior. Increasing evidence demonstrates a functionally relevant dissociation between DA cell body activity and striatal DA levels, highlighting the importance of local DA control. Given the reward-related activity of LTSIs, we explored whether LTSIs provide a novel mechanism of local DA regulation.

Methods: Anatomy: To probe for evidence of LTSI synapses onto DA axons, we injected SSTFlp/+;DATCre/+ mice with Flp-dependent Synaptophysin-mRuby in the DMS and Cre-dependent Synaptophysin-EGFP in the VTA/SN. After 6wks viral expression, we performed immunohistochemistry for tyrosine hydroxylase (TH) to visualize DAergic processes and imaged sections on a confocal microscope.

In vitro fast scan cyclic voltammetry (FSCV): LTSIs are tonically active in slice, so we tested the effects of bidirectional LTSI manipulations on optically evoked DA (oDA) in acute striatal slices. SSTFlp/+;DATCre/+ mice were injected with Cre-dependent channelrhodopsin in the VTA/SN to evoke oDA in all FSCV experiments. To test whether optogenetic LTSI inhibition alters oDA, one striatal hemisphere was injected with Flp-dependent halorhodopsin, the other with control Flp-dependent EGFP, and the effects of 617nm LED illumination tested. Separately, we chemogenetically excited LTSIs to explore the mechanism by which LTSIs locally gate DA. One striatal hemisphere was injected with Flp-dependent hM3DGq-mRuby, the other with control Flp-dependent mRuby, and the effect of 10uM clozapine-N-oxide (CNO) tested. After the oDA signal was stabilized in CNO, antagonists for GABA-A (picrotoxin, 100uM) or GABA-B (CGP55845, 2uM) were applied. FSCV experiments were conducted in the presence of 1uM DHBE and 1uM scopolamine to preclude any effect of cholinergic interneurons.

DA sensor during learning: We next assessed whether LTSIs modulate striatal DA during operant learning. SSTCre/+ mice were

injected with the GRAB-DA sensor and either Cre-dependent mRuby-Kir2.1 (an inwardly rectifying K+ channel that inhibits neuronal activity) or control Cre-dependent mRuby2 in the DMS and implanted with a fiberoptic cannula. DA sensor activity was recorded as mice learned a self-initiated operant task.

D2 partial agonist microinjection prior to learning: We tested whether LTSI-DA interactions underlie accelerated operant acquisition when LTSIs are inhibited. Aripiprazole is a D2 partial agonist that increases DA signaling when DA tone is low, but decreases DA signaling when DA tone is high. We hypothesized local aripiprazole administration would stabilize striatal DA levels between LTSI-inhibited and LTSI-control mice, suppressing the enhancement in learning rate mediated by LTSI inhibition. SSTCre/+ mice were bilaterally injected with either Cre-dependent ZsGreen-Kir2.1 or Cre-dependent EGFP and implanted with microinjection cannulae in the DMS. Aripiprazole (100ng/side) or vehicle was microinjected prior to operant acquisition.

Results: Anatomy: Some synaptophysin-mRuby puncta labeling LTSI synapses were co-localized with DA terminal synaptophysin-EGFP puncta and TH+ fibers, suggesting LTSIs make synapses onto DAergic processes in the DMS.

In vitro FSCV: Optogenetic LTSI inhibition augmented oDA release ($p < 0.001$), while chemogenetic LTSI excitation suppressed oDA release ($p < 0.001$). These interactions occur via GABA-B ($p < 0.01$), but not GABA-A.

DA sensor during learning: We revealed dynamic changes in DA signals across learning by aligning DA signals to discrete behavioral events during operant training. In early trials prior to acquiring the contingency, DA signals were circumscribed to the correct lever press and reward retrieval. As learning proceeded, DA signals connected to the correct lever press grew, while those aligned to reward retrieval decreased. LTSI inhibition did not alter the general progression of DA signals across learning, instead altering select signals at specific learning stages – prior to task acquisition, LTSI inhibition selectively amplified DA signals during reward ($p < 0.01$), but during and after task acquisition amplified DA signals to both reward ($p < 0.01$) and choice ($p < 0.05$).

D2 partial agonist microinjection prior to learning: Consistent with our prior work, LTSI inhibition accelerated learning in vehicle treated mice ($p < 0.05$). Striatal microinjection of aripiprazole normalized learning rates, preventing accelerated acquisition in LTSI-inhibited mice ($p < 0.05$) and accelerating acquisition in LTSI-control mice ($p < 0.05$).

Conclusions: These data demonstrate that LTSIs provide a novel mechanism for local modulation of dopaminergic signaling, acting via GABA-B to gate synaptically released DA. This dynamic regulation occurs both in slice and in vivo, and underlies the effects of LTSI inhibition on goal-directed learning. Corticostriatal connectivity drives action selection and performance, and plasticity in these circuits is critical for motor control and learning. We suggest that LTSIs act as local coordinators of corticostriatal plasticity, owing to their combined local modulation of DA as demonstrated here and dendritic inhibitory functions.

Keywords: Dopamine, Dorsal Striatum, Goal-Directed Behaviors, Striatal Dopamine Signaling, GABAergic Interneurons

Disclosure: Nia Therapeutics: Employee (Spouse)

T64. Astrocyte Glutathione S-transferases Regulate Microglial Activation and Neuronal Function During Brain Inflammation

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Background: Brain inflammation is a key pathological event in various neurological and psychiatric disorders. Emerging evidence has also highlighted an essential role of the xenobiotic defense system in immune responses at various tissues, including the brain. We have recently discovered that glutathione S-transferase mu 1 (GSTM1), an enzyme in the phase II detoxification system, was predominantly expressed in astrocytes and required for astrocyte-dependent microglia activation during LPS-induced brain inflammation in mice. In this study, we have examined the mechanisms by which GSTM1 regulates astrocyte activation and evaluated the impact of GSTM1 deficiency on neurons. We have also tested if GSTM1 is involved in aging or age-related neurodegenerative conditions using mice.

Methods: The effects of GSTM1 deficiency on astrocyte activation were evaluated by RNA-seq with in vitro cultured primary astrocytes. Co-immunoprecipitation experiments were conducted to explore potential targets of GSTM1. The influence of GSTM1 deficiency on neurons during inflammation was evaluated by challenging astrocyte-specific GSTM1 deficiency mice with systemic LPS administration. GSTM1 expression changes were further examined in the brains from aged mice and mice with Alzheimer's disease (AD)-associated genetic mutations.

Results: Astrocyte RNA-seq data revealed that GSTM1 is required to induce pro-inflammatory responses and suppress interferon responses. Consistent with this finding, GSTM1 was shown to directly interact with an active form of a component of NF-kB in astrocytes. In the brains of mice with LPS-induced brain inflammation, astrocytic GSTM1 deficiency resulted in increased cellular stress and decreased activity in nearby neurons. The expression of GSTM1 decreased in the frontal cortices of mice harboring AD-associated mutations while it increased in those of normal aged mice.

Conclusions: Our data suggest that GSTM1 in astrocytes is required to maintain neuronal homeostasis by remodeling its balance between pro-inflammatory and interferon responses. The data also indicate that astrocyte GSTM1 may be involved in protection against aging and that its loss might accelerate age-related neurodegeneration. Thus, our study provides a novel biological insight into the role of astrocytes in brain inflammation.

Keywords: Astrocyte, Inflammation, Aging, Microglia, Alzheimer's Disease

Disclosure: Nothing to disclose.

T65. Vortioxetine Reverses Cognitive Impairments Induced by Androgen Deprivation Therapy for the Treatment of Prostate Cancer in Young and Middle-Aged Healthy Rats

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Background: Androgen deprivation therapy (ADT) is a mainstay treatment for late-stage prostate cancer, but it is associated with several profound side effects, particularly severe cognitive impairment, observed in more than half of patients. Long-term occurrence of these impairments can significantly reduce quality of life for cancer survivors. The most prominent deficits observed in patients are in cognitive domains mediated by the medial prefrontal cortex (mPFC) and hippocampus (Hipp). Given the average age of onset in prostate cancer is around 65 years, it is likely that age can exacerbate these impairments. It is important to improve the cognitive side effects of ADT, as 10-year survival rate post treatment is over 97%. Vortioxetine is an FDA-approved antidepressant that has been shown to improve cognitive impairment in depression. Therefore, it may also be a novel therapeutic approach to alleviate ADT-induced cognitive decline.

We hypothesized that ADT will induce cognitive deficits in mPFC- and hippocampal-related cognitive tasks in healthy male rats, and age will exacerbate these impairments. Further, chronic treatment with vortioxetine will reverse these cognitive changes.

Methods: The gonadotropin releasing hormone antagonist degarelix, used clinically to treat prostate cancer, served as the chemical castration treatment in our ADT rodent model. Surgical castration was also used as a comparator. We tested young (3-month, 8-11/group) and middle-aged (12-month, 6-11/group) male rats, at which age-related cognitive impairments are just beginning to emerge. Male Sprague-Dawley rats were surgically castrated or injected with 3 mg/kg degarelix at a concentration of 30 mg/mL (dissolved in 5% mannitol). Controls received either a sham surgery or a vehicle injection of 5% mannitol. Following the ADT procedure, all animals were singly housed. Beginning 10 days after surgery or degarelix, rats were administered vortioxetine in their diet (28 mg/kg/day) or control chow for 21 days. Animals were food restricted 7 days prior to behavioral testing using the novel object location (NOL) test and the attentional set-shifting test (AST). Upon completion of behavior, tail vein blood samples were taken to confirm levels of testosterone. Three-way ANOVA, followed by Tukey's multiple comparison test, was used to analyze all behavioral experiments (GraphPad Prism 8, San Diego, USA). All procedures were approved by the University of Texas Health San Antonio Institutional Animal Care and Use Committee and complied with National Institutes of Health guidelines.

Results: There were no baseline differences between young sham-control and middle-aged sham-control animals in visuospatial memory on the NOL test. Castration impaired visuospatial memory in young animals, and trended toward a similar impairment in aged animals (young $p < 0.01$, $d = 0.514$). Aged animals are still being tested to achieve sufficient power to detect any potential exacerbation due to age in castrated animals. Vortioxetine fully reversed the impairment in visuospatial memory in young rats and appears to improve cognitive decline in aged animals, again still preliminary (young $p < 0.05$, $d = 0.610$). On the AST, there were also no baseline differences in performance between young control and middle-aged control rats. On the mPFC-mediated set-shifting task, castrated rats displayed deficits in comparison to age-matched controls (young $p < 0.001$, $d = 0.729$;aged $p < 0.05$, $d = 0.381$), and vortioxetine reversed these effects (young $p < 0.001$, $d = 0.825$; aged $p < 0.05$, $d = 0.677$). Although age did not appear to exacerbate changes in cognition due to castration on the set-shifting task, there was an age-induced exacerbation of castration effects on the reversal learning task of the AST (young cast/cntl compared to aged cast/cntl, $p < 0.01$, $d = 0.502$). This is noteworthy, as young castrated animals did not display a deficit in reversal learning (young sham/cntl vs young cast/cntl, $p > 0.999$). In aged rats, vortioxetine reversed the deficit back to intact control levels (aged cast/cntl compared to aged cast/vortioxetine, $p < 0.05$, $d = 0.567$). Studies with degarelix are still underway, but preliminary results reveal that degarelix also compromises cognitive function on both the NOL and AST and vortioxetine reverses these effects.

Conclusions: Our results indicate that vortioxetine reversed ADT-induced cognitive decline in domains mediated by both the mPFC and Hipp. Additionally, vortioxetine was effective in a middle-aged rodent model, indicating that it could be useful in mitigating cognitive changes in older men treated for prostate cancer. The potentially detrimental effects of cancer, which can promote inflammatory processes, on cognition, and its interaction with the effects of cancer therapy will be tested in this model in future studies. In summary, these studies identify a possible therapeutic intervention for the treatment of cognitive impairment induced by ADT.

Keywords: Cognition, Medial Prefrontal Cortex, Dorsal Hippocampus, Testosterone, Novel Antidepressant

Disclosure: Nothing to disclose.

T66. Regulation of Associative Memory by Presynaptic mRNA Transcripts

Abstract not included.

T67. Effects of Biological Sex and Circulating Sex Hormones on Oxidative Stress

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Background: Oxidative stress, an imbalance between the production of reactive oxygen species and available antioxidant capacity, is implicated in psychiatric disorders including bipolar disorder, schizophrenia, depression and anxiety disorders. Critical factors involved in the mechanistic pathway of oxidative stress include biological sex and sex hormones, particularly estrogens given their antioxidant properties. Pre-clinical and peripheral studies suggest that oxidative stress differs by biological sex and covaries with circulating estrogens. However, studies have not yet examined the relationship between biological sex, circulating sex hormones and in vivo measurements of oxidative stress in the brain. Therefore, we aimed to test these relationships with peripheral and regional concentrations of glutathione (GSH), the primary antioxidant in the brain.

Methods: At Brigham & Women's Hospital 10 women and 5 men participated, ages 37–58 ($M = 46.93$, $SD = 7.19$). At Johns Hopkins, 5 women and 7 men participated, ages 35–64 ($M = 47.83$, $SD = 9.21$). MR spectroscopy, using STEAM at 7 Tesla (TE = 20ms, TM = 10ms, TR = 3000ms), was used to assess central GSH at both sites and LCModel was used for GSH quantification. Regions of interest included the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (VMPFC), and dorsolateral prefrontal cortex (DLPFC). Peripheral total GSH was also assayed. To assess the relationship between biological sex and GSH, we conducted a standard effect size z-score meta-analysis across the two research sites. Additionally, sex hormone assays were performed on the dataset from Brigham and Women's Hospital to assess levels of estradiol, estrone, and progesterone. We conducted separate regression analyses to assess individual circulating sex hormones as predictors of peripheral GSH and central GSH in the three regions of interest in women. In each of the models we included age as a control covariate and significance was assessed at $p < 0.05$ alpha level and standardized beta coefficients are reported for significant results.

Results: We observed a significant difference in VMPFC GSH depending on biological sex with males displaying higher levels of GSH in the VMPFC ($z = -2.10$, $p = 0.04$). We did not observe sex differences in peripheral GSH ($z = -0.56$, $p = 0.58$), ACC GSH ($z = 0.41$, $p = 0.68$), or DLPFC GSH ($z = -0.49$, $p = 0.62$). For analyses investigating circulating sex hormones in women and GSH, we found significant effects related to ACC GSH. For GSH in the ACC, estradiol was significantly associated ($b = -.82$, $t = -3.45$, $p = 0.01$). Similarly, estrone was significantly associated with GSH ($b = -0.74$, $t = -2.90$, $p = 0.02$) in the ACC. Progesterone ($F = 1.87$, $p = 0.22$) was not significantly associated with ACC GSH. No other significant results were observed in testing the relationships of circulating sex hormones with GSH in the DLPFC, VMPFC or peripheral GSH.

Conclusions: These results suggest that biological sex and circulating sex hormones in women are key factors to consider in relation to oxidative stress. Biological sex was shown to be related to VMPFC GSH, and circulating sex hormones, estradiol and estrone, were shown to be related to GSH in the ACC, an effect

that remained significant while adjusting for age. In contrast, neither biological sex nor circulating sex hormones appeared to have a strong relationship with peripheral GSH. Despite the promising nature of these preliminary findings, they should be interpreted with caution given the small sample size. Notwithstanding, these results advocate for the need to account for the relationship of circulating sex hormones and biological sex with oxidative stress. If confirmed, these findings have the potential to inform clinical care regarding the use of antioxidant or estrogenic medications to improve outcomes in psychiatric conditions. Furthermore, these results have broad implications for women's brain health thereby informing potential sex specific interventions.

Keywords: Sex Hormones, Sex Differences, Oxidative Stress, Magnetic Resonance Spectroscopy, Anterior Cingulate Cortex (ACC)

Disclosure: Nothing to disclose.

T68. Sex-Specific Differences in the Association Between Obesity and Brain Aging in Young Adults: Findings From the Human Connectome Project

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Background: There are various complications related to obesity such as heart disease, diabetes and psychiatric conditions, and furthermore obesity may compound the morbidity and mortality associated with these complications. Emerging evidence in middle aged and elderly individuals suggests that obesity may be associated with accelerated brain aging. However, there is limited information on the impact of obesity on brain aging in young adults. Furthermore, while sex differences in pathophysiology of mental illnesses have gained recent attention, whether obesity affects brain aging differentially in males versus females has not been studied systematically. In this report, we evaluated the sex-specific differences in the association between brain aging and obesity in young adults using the publicly available data from the Human Connectome Project (HCP).

Methods: Participants of HCP with structural imaging and body mass index (BMI) data available were included ($n = 1112$; mean age = 28.80; sd = 3.70). Predicted brain age was generated using raw T1-weighted MRI scan and a Gaussian Processes regression model as described by Cole et al (Molecular Psychiatry 2018; 23: 1385-1392). We computed the difference between chronological age and brain age predicted by structural imaging [Δ aging = (chronological age) – (predicted brain age)]. Lower values of Δ aging suggest greater brain aging. We used a generalized linear model with Δ aging as the dependent variable, and sex, BMI and BMI-by-sex interaction and the independent variables of interest and race, ethnicity, income, and education as covariates.

Results: We found a significant BMI-by-sex interaction for Δ aging ($p = 0.046$). Higher BMI was associated with greater brain aging in both males and females. However, this association was two-times stronger in males ($\beta = -0.23$; 95% CI of -0.33 to -0.13) than in females ($\beta = -0.13$; 95% CI of -0.19 to -0.06).

Conclusions: We found evidence suggesting that obesity is associated with greater brain aging in young adults. Furthermore, the association between obesity and brain aging was stronger in males than in females. Future studies are needed to explore the mechanistic pathways that link obesity to brain aging and whether weight-loss interventions, such as exercise, can reverse obesity-associated brain aging.

Keywords: Brain Age, Obesity, Sex Difference

Disclosure: Nothing to disclose.

T69. 7T Functional Magnetic Resonance Spectroscopy of Metabolite Variations During Working Memory in Trauma-Exposed Individuals

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Background: People with PTSD commonly report difficulties with working memory, yet the neural basis of its dysfunction is not well understood. Previous fMRI studies of PTSD have shown reduced activation in the dorsolateral prefrontal cortex (DLPFC), a crucial brain region for working memory. Converging evidence from animal models and human studies points to glutamatergic dysfunction in key brain regions in PTSD. Thus, it is possible that neurometabolic abnormalities could underlie the differential activation patterns observed in the DLPFC; however, this has not been directly tested. Functional magnetic resonance spectroscopy (fMRS) can potentially address this issue by measuring neurometabolite changes associated with neural activity in response to stimuli. In this ongoing study, we are using 7T resting-state MRS as well as fMRS during the N-back working memory task to measure neurometabolite changes in the DLPFC of people with PTSD, trauma-exposed people without PTSD, and non-trauma-exposed controls. We hypothesize that (1) glutamate is reduced in people with PTSD, (2) glutamate increases with working memory load, and (3) working memory load interacts with the group-glutamate association.

Methods: 6 trauma-exposed people without PTSD (TEC; age: 20.8 +/− 2.6; sex: 3 F / 3 M) and 9 people without trauma exposure (CON; age: 26.6 +/− 10.8; sex: 7 F / 2 M) were included in this preliminary analysis. Imaging was performed at the Auburn University MRI Research Center on a Siemens MAGNETOM 7T MRI scanner equipped with a 32-channel head coil. 3D MPRAGE structural images were obtained for voxel placement. Spectra were acquired from the left DLPFC (25x25x25 mm) using an ultra-short TE STEAM sequence (TR/TE/TM = 10,000/5/45 ms), FASTESTMAP shimming, and VAPOR water suppression. For resting-state MRS, 32 averages with water suppression and 4 averages without water suppression were acquired. fMRS was acquired while participants completed the N-back task. Stimuli were single letters presented one at a time. The task included 9 alternating blocks of 0-back, 1-back, and 2-back conditions (3 blocks of each working memory load). For fMRS, 8 water-suppressed averages were acquired during each block, which were combined in MATLAB using in-house code. MRS and fMRS spectra were analyzed in LCModel using a simulated basis set. Spectra were eddy current corrected and quantified using the unsuppressed water signal. MRS levels of glutamate were compared between groups using one-way ANOVA. fMRS levels of glutamate were averaged within each condition, and then repeated measures ANOVA was used to examine the effect of group, working memory load, and group by load interaction. We also investigated glutamine and GABA in exploratory analyses.

Results: We observed no group differences in resting-state MRS levels of glutamate ($F(1,13) = 2.598$, $p = 0.131$, partial eta squared = 0.167), glutamine ($F(1,13) = 1.585$, $p = 0.230$, partial eta squared = 0.109), or GABA ($F(1,13) = 1.520$, $p = 0.239$, partial eta squared = 0.105). We excluded 1 TEC and 2 CON from the fMRS analyses due to poor spectral quality; therefore, fMRS analyses included 5 TEC and 7 CON. For fMRS measures of glutamate, we found no significant effects of group ($F(1,10) = 0.006$, $p = 0.941$, partial eta squared = 0. 001), working memory load ($F(2,20) = 1.502$, $p = 0.247$, partial eta squared = 0.131), or group by load interaction ($F(2,20) = 1.628$, $p = 0.221$, partial eta squared = 0.140). For glutamine, we observed a significant effect

of working memory load ($F(2,20) = 3.657$, $p = 0.044$, partial eta squared = 0.268) and a significant group by load interaction ($F(2,20) = 3.791$, $p = 0.040$, partial eta squared = 0.275), such that glutamine levels were higher in the TEC group during 2-back versus 1-back when compared to the CON group. For GABA, we observed a trend for an effect of working memory load ($F(2,20) = 2.950$, $p = 0.075$, partial eta squared = 0.228), such that GABA levels tended to increase with greater working memory load.

Conclusions: In this preliminary analysis, we observed metabolite changes during working memory in trauma-exposed people without PTSD compared to people without trauma exposure. In future work, we will include participants with PTSD as well as brain activation data from fMRI. Since fMRS and fMRI probe different aspects of neuronal firing and synaptic activity, the combined approach of these techniques could better characterize the neurobiology underlying cognitive deficits in PTSD.

Keywords: Trauma Exposure, Functional Magnetic Resonance Spectroscopy, 7T, Working Memory

Disclosure: Nothing to disclose.

T70. Pre-treatment Neural Function During Emotional Processing Predicts Improvement in Anxious Adolescents

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Background: Anxiety disorders are among the most common mental health conditions affecting children and adolescents and rank among the biggest drivers of health care burden for individuals under the age of 18. Brain activation during emotional processing is altered in multiple regions within prefrontal-amygdala circuitry. However, there are few data on how activity within this circuitry prior to treatment might predict either the magnitude or trajectory of response to common treatments, including selective serotonin reuptake inhibitors (SSRIs). Examining this is important to understanding SSRI mechanism of action and to identifying patients who require alternative interventions. With this in mind, we sought to identify pre-treatment [is it just pre-treatment brain activation during emotional processing and how it might predict later improvement in anxiety symptoms in adolescents with generalized anxiety disorder (GAD).

Methods: We conducted an 8-week, double-blind, controlled trial in adolescents with GAD in which patients were randomized (1:1) to escitalopram ($n = 26$) or placebo ($n = 25$) at an outpatient, single site, academic medical center. Patients were medication-free adolescents aged 12-17 years with a primary diagnosis of GAD based on the Anxiety Disorders Interview Schedule for DSM-IV-TR (ADIS-IV) and had a Pediatric Anxiety Rating Scale (PARS) score ≥15 and a clinical global impression-severity score ≥4 at baseline. To examine functional activation in response to emotional processing, patients performed the continuous processing task with emotional and neutral distractors (CPT-END) in the scanner. During this task, patients responded to emotional or neutral pictures or square or targets (circles). The task consisted 2 runs, each run containing 158 pictures (square 70%, circle 10%, emotional picture 10%, and neutral picture 10%) with an onset-to-onset interval of 3000 ms and a duration of 2750 ms, a fixation cross was presented in the interval between pictures for 250 ms. Functional images and high-resolution anatomical images were obtained with a 3-Tesla scanner (Achieva; Philips, USA) with a 32-channel phased-array head coil. Functional images were pre-processed in SPM12 for spatial realignment, slice-timing, coregistration, normalization, and 8-mm Gaussian imaging smoothing. Patients who did not complete the scan or had excessive movement >3 mm or 3 degrees were excluded (placebo: $n = 8$; escitalopram: $n = 7$). First-level, within-subject analysis was performed with a general linear model with four regressors: circle, emotional, neutral, and square. Six motion parameters were included as nuisance regressors to correct for motion artifacts. For each participant, contrast images of emotional and neutral pictures were generated. Percent blood oxygen level dependent (BOLD)-signal change in the amygdala, ventrolateral prefrontal cortex (VLPFC), medial prefrontal cortex (mPFC) and dorsal anterior cingulate (dACC) in response to emotional (relative to neutral) images was extracted. Then, logarithmic mixed effects models (using Julia, version 1.0), were employed to examine the relationship between baseline activation for each ROI and the trajectory of anxiety improvement (PARS score) using week 0, 1, 2, 4, 6 and 8/early termination(ET) ratings. These models included age and sex as covariates and findings were considered significant at the $p < 0.05$ threshold.

Results: Patients who received escitalopram ($n = 19$) and those who received placebo ($n = 17$) did not differ statistically in terms of age (mean escitalopram, 14.5 ± 1.6 years; mean placebo: 15.2 ±1.5 years, $p = 0.18$), IQ, gender (escitalopram: 4 males; placebo 6 males, $p = 0.46$) and baseline anxiety severity ($p = 0.77$). In patients who received escitalopram, the change in anxiety over 8 weeks of treatment was predicted by baseline activation to emotional stimuli in left amygdala (left: $p = 0.007$, right: $p = 0.363$), right VLPFC (left: $p = 0.398$; right: $p = 0.031$), but not the mPFC (left: $p = 0.0623$; right: 0.931) or dACC (left: $p = 0.052$; right: $p = 0.3972$). In patients who received placebo, activation to emotional stimuli in the right amygdala (left: $p = 0.843$; right: $p < 0.001$), left mPFC (left: $p = 0.004$; right: $p = 0.134$) and right VLPFC (left: $p < 0.097$; right: $p < 0.001$) but not the dACC (left: $p = 0.380$; right: $p = 0.803$) predicted the trajectory of change in anxiety symptoms.

Conclusions: In adolescents with GAD, baseline activation of the amygdala, VLPFC and mPFC predicts the magnitude of subsequent improvement in anxiety. These findings raise the possibility that pre-treatment amygdala-prefrontal activation could identify patients more likely to respond to treatment and emphasizes the importance of amygdala-prefrontal circuitry as a target for pharmacotherapy in this population.

Keywords: Anxiety, fMRI, SSRI

Disclosure: Allergan, Neuronetics: Grant (Self); FDA: Advisory Board (Self); Springer: Royalties (Self); Neuroscience Education Institute, CMEology: Honoraria (Self); Intracellular Therapeutics, Myriad Genetics: Consultant (Self)

T71. Organization Effects of Gonadal Hormones During Puberty Cause Sex Differences in Social Anxiety Behavior

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Background: About 20% of US adults will be diagnosed with an anxiety disorder in their lifetime, making anxiety the largest mental health concern today. Women in particular face higher risks and are 2 times more likely to be diagnosed with an anxiety disorder then men. Interestingly, this sex difference does not extend to childhood anxiety and only begins to emerge at the start of puberty. Work in rodents has also found larger social anxiety response in adult females vs. males. However, adult castration does not eliminate this sex difference indicating that any hormonal effects across puberty may be organizational instead of activational.

Here I use the California mice (Peromyscus californicus) model to investigate the effects of pubertal hormones on social anxiety. Both male and female California mice will naturally exhibit high

levels of aggression toward same sex conspecifics, allowing for a direct comparison of social stress in males and females.

Here I present original, unpublished data on sex differences in juvenile California mouse social anxiety behavior, the impact of an oxytocin receptor antagonist (OTA) on juvenile social anxiety behavior, and organizational effects of male pubertal hormones on adult male social anxiety behavior. By the time of presentation, I anticipate the addition of preliminary data on the effects of male pubertal hormones on androgen versus estrogen receptors.

Methods: Experiment 1: Juvenile males and females were randomly assigned to defeat vs. control conditions (n = 6-9). Defeat consisted of 3 consecutive days to exposure to a novel same sex aggressor for 7 minutes or until the test mouse had received 7 bites. Control mice underwent comparable handling. 2 weeks after social defeat mice underwent social interaction testing. Anxiety behavior was measured via: 1) interaction time-time investigating a novel mouse, 2) vigilance- time the test mouse spent still with its head oriented toward the novel mouse but not in proximity.

Experiment 2: Juvenile males and females underwent 3 episodes of social defeat and social interaction testing 2 weeks later. Mice were randomly assigned to receive either an i.p. injection of saline, 5mg/kg, 10mg/kg of the OTA L-368,899 30 minutes prior to social interaction testing (n = 5-9).

Experiments 3/4: Prepubertal castrations, control sham surgeries, or no surgery control occurred on post-natal day 40. After reaching adult maturity mice underwent social defeat and social interaction testing as described above (n = 6-8). Mice to receive a hormone replacement implant will receive their implant on the same day as castration surgery.

All juvenile mice completed testing by post-natal day 50, which marks the beginning of early adolescents in California mice. All adult mice started testing after post-natal day 90, which marks the beginning of adult maturity.

Statistical analysis: all data was normalized when appropriate followed by ANOVA testing and pairwise comparison post-hoc analyses.

Results: Experiment 1: Social defeat stress had a significant effect on interaction time in both males and females ($p < 0.001$) with defeated mice of both sexes showing decreased interaction compared to control ($p < 0.001$ for both). Social defeat also had a significant effect on vigilance ($p < 0.001$) with defeated males ($p < 0.03$) and females ($p < 0.001$) showing increased vigilance compared to control.

Experiment 2: Social interaction data finds both effects of OTA ($p < 0.01$) and sex ($p < 0.05$). Males treated with 5mg/kg of OTA show increased social interaction when compared to control ($p < 0.05$) and 10mg/kg treated males ($p < 0.01$). However, there is no significant effect of OTA in females. Vigilance data finds an effect of OTA ($p < 0.05$), with 5mg/kg treated females showing significantly less vigilance than control ($p < 0.01$). 5mg/kg treated males show a trend for less vigilance than control ($p = 0.08$) and significantly less than 10mg/kg treated males ($p < 0.03$).

Experiment 3: Social interaction data finds both effects of castration ($p < 0.05$) and social defeat ($p < 0.01$). Castration mice who underwent defeat show decreased interaction compared to castrated controls ($p < 0.01$), defeated sham surgery ($p < 0.02$), and defeated no surgery ($p < 0.02$). Vigilance data finds a trend for castration ($p = 0.06$) and an effect of social defeat ($p < 0.02$). Castration mice who underwent defeat show increased vigilance compared ton castrated controls ($p < 0.01$), defeated sham surgery ($p < 0.03$), and defeated no surgery ($p < 0.05$).

Conclusions: Juvenile California mice do not show sex differences in social anxiety behavior, and it is only after exposure to gonadal hormones during puberty that males exhibit lower levels of anxiety behavior. This mirrors trends seen in humans where there are no sex differences in rates of childhood anxiety but higher rates of diagnosed anxiety disorders in adolescent and adult women. OTA manipulation in juveniles show that oxytocin plays an important role in social anxiety behavior, as it does in adults.

Keywords: Puberty, Social Anxiety, Neuroendocrine, Testosterone, Sex Differences

Disclosure: Nothing to disclose.

T72. Association Between Inflammation and Increased Alcohol Dependence Rather Than Consumption in Those With PTSD

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Background: Post-traumatic stress disorder (PTSD) and Alcohol Use Disorder (AUD) are highly prevalent and often comorbid in both the general population, as well as among combat Veterans. AUD prevalence among those with PTSD is 28% for women and 52% for men, while rates of PTSD among patients with AUD are 30-59%. Currently, we do not understand the biological mechanisms promoting the development of AUD in some PTSD patients, which will require high-resolution prospective studies in understanding development vs. maintenance of symptoms of each disorder. Evidence supports a role for inflammation as a potential pathophysiological mechanism underlying both PTSD and AUD. C-reactive protein (CRP) specifically has been identified as a risk factor for PTSD, while chronically elevated blood alcohol levels can increase CRP. Alcohol craving and consumption are associated with elevated plasma levels of inflammatory cytokines in alcoholics. Here we tested the hypothesis that inflammation, as measured by CRP, may interact with PTSD symptoms to predict alcohol dependence behaviors over 6 months post-combat deployment.

Methods: In a study of combat trauma in active duty service members (Marine Resiliency Study), Marines and Navy Corpsmen (N = 1890) were given the AUD Identification Test (AUDIT) as well as the Clinician-Administered PTSD Scale (CAPS) both 3 and 6 months after a combat deployment to Afghanistan or Iraq. AUDIT scores were totaled separately for alcohol consumption (i.e., frequency and quantity of drinking) and dependence behaviors (i.e., difficulty controlling drinking and functional impairment). Plasma was collected for the measurement of CRP by enzyme-linked immunosorbent assay. Associations between PTSD, AUD, and CRP at both post-deployment time points were analyzed using linear regression or zero-inflated negative binomial regression (ZINBR), to account for skewing from excess zero responses in the AUDIT score.

Results: While a PTSD diagnosis predicted alcohol consumption at 3-months (N = 1446; $p < 0.01$) post-deployment, there were no main effects of CRP or interactions, PTSD diagnosis predicted a 35% lower chance of demonstrating zero dependence (N = 1446, $p < 0.001$, ZINBR zero model) at 3-months post-deployment, as well as a roughly 10% lower chance of demonstrating zero dependence (N = 1190, $p < 0.001$, ZINBR zero model) at 6-months post-deployment. In those endorsing dependence symptoms, PTSD diagnosis alone did not predict dependence severity but did interact with CRP to predict dependence severity at 3-months (N = 353, $p < 0.02$, count model regression) and at 6-months post-deployment (N = 259, $p < 0.05$, count model regression), with increasing CRP associated with increased dependence symptoms only in the PTSD group. Similar findings were found using total CAPS severity scores instead of PTSD diagnosis. It should be noted that of those reporting at least some dependence behaviors (>0), symptom severity in subjects with PTSD was 3.50 (range= 1–10) at 3-months post-deployment and 4.25 at 6-months post-deployment. At the same time, those without PTSD averaged 2.90 (range=1–10) ($p > 0.5$) at 3-months post-deployment and 2.84

(range= 1–10) at 6-months post-deployment, suggesting that the association of CRP with dependence severity in the PTSD group initially at 3-months is not simply due to greater alcohol dependence in that group.

Conclusions: These data support the hypothesis that there is a synergistic relationship between PTSD and CRP associated with higher alcohol dependence but not consumption. These effects may be mainly driven by the relationship between CRP and numbing PTSD symptomatology. Although directionality cannot be inferred from these preliminary data, one possibility is that PTSD, in combination with inflammation, may increase vulnerability for alcohol use. Interestingly, similar amounts of dependence symptoms occurred between individuals with and without PTSD, indicating that higher inflammation is not merely an artifact of higher dependence in the PTSD group. Future longitudinal analyses, as well as studies with animal models, will provide a greater mechanistic understanding of potential causal relationships between inflammation, trauma, and alcohol dependence.

Keywords: CRP, Combat PTSD, Alcohol, PTSD, Inflammation

Disclosure: Nothing to disclose.

T73. Evidence of Autonomic Hypersensitivity and Blunted Ventromedial Prefrontal Cortex Activity During Interoceptive Perturbation in Generalized Anxiety Disorder

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Background: Generalized anxiety disorder (GAD) is characterized by uncontrollable anxiety and worry leading to heightened autonomic arousal and apprehensive expectation regarding such arousal states. Although GAD individuals often report somatic symptoms, autonomic hyperarousal symptoms are often considered less prominent than in other anxiety disorders (e.g., panic disorder). Using peripheral beta-adrenergic stimulation via bolus infusions of the fast-acting adrenaline analog, isoproterenol, we examined the degree to which measures of cardiorespiratory interoception, and their neural and behavioral correlates, differ between GAD and healthy comparisons (HC).

Methods: Females with GAD ($n = 29$) and female HCs ($n = 29$) matched for age and BMI received randomized double-blinded bolus infusions of isoproterenol (0.5, 2 micrograms) and saline during BOLD fMRI scanning at 3 Tesla. Panic disorder was exclusionary. Participants concurrently rated their cardiorespiratory sensation intensity using a dial during infusions and afterward via self-report. We tested for group differences in peripheral sensitivity with a *t*-test comparing the chronotropic dose 25 (CD25), an indirect measure of beta-adrenergic receptor density, which is defined by the minimum dose required to raise the heart rate by 25 beats-per-minute. Using linear mixed-effects models (LME) with age and BMI covariates, we assessed the effect of dose and group on physiological (heart rate and respiratory volume variability) and subjective (real-time cardiorespiratory dial rating) responses during discrete physiologically-relevant windows (e.g., peak response and early recovery periods). We subsequently assessed retrospective perceptions of cardiorespiratory sensation and experienced anxiety after each dose. We conducted whole-brain fMRI to assess group effects on subject-level contrast maps associated with each response period at a voxel-wise threshold of $p < 0.001$ (cluster corrected at a 5% false-positive rate, analyses in AFNI). Next, to evaluate the effect of isoproterenol on the overall time course of heart rate, dial ratings, and regional BOLD responses, we applied a multivariate Functional Principal Components Analysis (mFPCA) to these signals. Using spline basis functions, each individual's response was modeled in a multivariate fashion via a matrix of spline coefficients characterizing the major modes of variation around the smoothed mean trajectory. We examined the effects of dose and group (and their interaction) on each signal's mean time course by entering coefficients from the mFPCA that summarized two principal components (PC) of the trajectories into an LME analysis. We selected region-of-interest (ROI) brain BOLD responses within the salience (insula/ACC/amygdala) and default-mode (vmPFC/dmPFC) networks defined by a probabilistic cytoarchitectonic atlas (Fan et al. 2016).

Results: Female GAD subjects exhibited lower CD25 values than HCs indicative of peripheral hypersensitivity to isoproterenol ($p = 0.04$, Cohen's $d = 0.55$). Greater heart rate responses to the 0.5 mcg dose drove this effect (group by dose interaction during the peak response period, $p = 0.002$). Real-time dial ratings also differed at 0.5 mcg (group by dose interaction during peak and early recovery, $p \leq 0.01$). GADs retrospectively reported heightened anxiety across all doses ($p \leq 0.005$), and heightened heartbeat ($p < 0.001$) and respiration ($p \leq 0.001$) intensity at the 0.5 mcg dose relative to HCs. The whole-brain analysis showed the insular cortex to be most active during anticipation and receipt of isoproterenol across both groups, replicating our previous studies (Hassanpour et al. 2016, 2018), but there were no group differences in activation of this region. Rather, the GAD group exhibited attenuated vmPFC activity relative to HCs during the peak and early recovery periods for the 0.5 mcg dose ($p < 0.05$ corrected). LMEs of the PC trajectories largely corroborated the whole-brain results and LMEs of univariate data: PC coefficients describing the trajectory of heart rate and dial ratings revealed an effect of the 2 mcg dose on both PCs for heart rate ($p < 0.001$) and dial response ($p \leq 0.004$). At 0.5 mcg, a dose-effect was seen on the first PC for HR ($p = 0.008$), while a group by dose interaction was seen for dial responses ($p = 0.039$). BOLD PC trajectories showed a similar pattern, with at least one PC from each ROI showing a significant dose-effect at 2 mcg ($p \leq 0.015$). Moreover, a group by dose interaction was observed on the first PC for both the vmPFC ($p = 0.036$) and amygdala ($p = 0.03$) at 0.5 mcg, and at the 2 mcg dose for the amygdala ($p = 0.042$). A group effect was also seen for the second PC of the vmPFC and caudate.

Conclusions: During adrenergic stimulation, females with GAD showed an autonomic hypersensitivity characterized by greater elevations in heart rate. These responses were accompanied by, heightened interoceptive awareness, anxiety, and a blunted neural response in the vmPFC, a brain region related to self-referential processing and visceromotor control. Our results provide strong evidence that, in females, 1) GAD constitutes a failure to appropriately appraise and regulate sympathetic arousal signals, and 2) both the autonomic and central nervous systems contribute to GAD interoceptive pathophysiology. Further progress in explaining GAD pathophysiology will require a better understanding of the causal interactions between both systems, and whether sex differences contribute to interoceptive dysfunction in GAD.

Keywords: Anxiety, Interoception, Generalized Anxiety Disorder, Ventromedial Prefrontal Cortex, Amygdala

Disclosure: Nothing to disclose.

T74. Circuit and Molecular Architecture of a Ventral Hippocampal Network

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Background: Over the last decade, the ventral portion of the hippocampus (vHPC) has been increasingly recognized as a critical node in the extended limbic circuitry that controls motivated and emotional behavior. The nature of the region's functions – e.g. controlling anxiety-related behaviors, influencing reward seeking behavior, and modulating the neuroendocrine response to stress have stoked considerable interest in vHPC's potential contributions to mood and anxiety disorders. While recent studies have indicated that ventral CA1 (vCA1) projection neurons are functionally dissociable, the basic principles of how the inputs and outputs of vCA1 are organized remain unclear. Here we used viral and sequencing approaches to define the logic of the extended vCA1 circuit.

Methods: We performed high-throughput single neuron tracing using multiplexed analysis of projections by high throughput sequencing (MAPseq). A MAPseq barcode library was injected into the vCA1 then 44 hours later were rapid decapitated, sectioned on a cryostat, and tissue punches were collected from target areas (PFC, NAc, LS, BNST, LH, BA, and CeA) and vCA1, then samples were sequenced. We then used input output tracing for determining the input pattern to vCA1; animals were injected with AAV2retro-Cre into the same target areas, followed by injection of rabies viruses, and whole brain input to projection defined vCA1 neurons was analyzed. Finally, we used transcriptional profiling methods that accessed translating mRNAs in vHPC neurons defined by their projection to one of these four targets.

Results: Through our MAPseq studies of vCA1 we identify a population of neurons that simultaneously broadcast information to multiple areas known to regulate the stress axis and approach/avoidance behavior. We found that ~77% (1920/2494) of barcoded vHPC neurons projected to only one of the assayed target regions. And of the ~23% that projected to multiple targets, ~18.2% (453/2494) sent axons to two targets, ~3.7% (93/2494) to three targets, and ~1.1% (28/2494) to greater than three of the assayed targets. We next determined whether vHPC output neurons previously implicated in approach/avoidance behavior and fear learning receive long-range, extra-hippocampal inputs from similar or diverse upstream regions. Identifying vCA1 cells that extend axons to mPFC, NAc, LS, BNST, BA, LH – we catalogued these neurons' patterns of long-range inputs using "tracing the relationship between input and output" (TRIO) method. First, while all projection neurons received thalamic input, most notably input from the paraventricular nucleus of the thalamus, TRIO suggested that vCA1-LH projection neurons receive proportionally more input from PVT than the projections to BA and mPFC. Second, TRIO predicted that vCA1-BA projection neurons get proportionally more input from the basal forebrain, most notably from the nucleus of the diagonal band than vCA1-LS and vCA1-BNST projections. And third, TRIO predicted that vCA1-BNST projection neurons get proportionally more input from the lateral amygdala that the other projections assayed. Finally, we determined whether vCA1 neurons projecting to the LH, NAc, BA and mPFC differ in terms of the genes they express. Pairwise comparisons of vCA1 projections between each vCA1 projection neuron type revealed 24 genes that were significantly differentially expressed. Interestingly however, these comparisons revealed a unique transcriptional profile in vCA1-mPFC projections relative to other subcortical projections where we found 653 genes that were differentially expressed (pAdj < 0.05).

Conclusions: Together, these data enrich our understanding of the organization of the vCA1, showing how neurons there are differentially connected to upstream inputs, how activity there is disseminated to downstream areas and how neurons display subtly different molecular identities. We find that vCA1 projections show not only show a one-to-one connectivity with downstream areas, but that a significant fraction of neurons project to multiple downstream areas in a non-random fashion. In addition, we find that overall, these six groups of output neurons received a similar distribution of inputs from upstream subcortical areas, with a few differences in the proportion of those inputs. Finally, analysis of translating mRNAs found a gene expression signature that differentiates vCA1-mPFC projectors from those neurons that project to LH, BA and NAc. These data not only provide future opportunities for targeting these classes of cells for visualization and manipulation, but by providing unique molecular signatures of cell-types with distinct functions, they may provide new avenues for testing new therapeutic targets.

Keywords: Anxiety Circuitry, Ventral Hippocampus, Neuronal Tracing

Disclosure: Nothing to disclose.

T75. Clustering of ASD Subjects Using Autism Behavior Inventory (ABI) Scales

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Background: The autism Behavior Inventory (ABI) was recently developed as a novel, web-based, parent or caregiver rating scale for assessing ASD core symptoms and associated behaviors over a 1-week recall period1. The reliability and validity of ABI in clinical populations has been presented elsewhere1. The current assessments evaluate potential use of the ABI to subtype ASD subjects.

Methods: Unsupervised clustering algorithms were applied on baseline ABI data from ASD subjects to assess the ability of the ABI to group patients. Data included patients from both a clinical trial ($N = 141$) and a research center ($N = 42$). The 5 ABI domain scores, ABI core scores and age were used to perform model based2 and hierarchical clustering3. The tendency to cluster was assessed using Hopkins statistic4 and visual assessments5. The optimum number of clusters was evaluated using the elbow method, the silhouette method and gap statistics6. The clusters were characterized from clinical trial subjects using existing scales including Social Responsiveness Scale (SRS), IQ (verbal, non-verbal and composite) and Autism Diagnostic Observation Schedule (ADOS) (Restrictive Repetitive Behavior (RRB), Social Affect and Total scores).

Results: The range of the median values was 0.5 (ABI Challenging Behavior) to 1.14 (ABI Core), indicating that ASD subjects were in the low to moderate end for defined ABI scores of 0-3. Based on the Hopkin's statistic (2) (0.31) and the visual assessment, the tendency to cluster was moderate, with two clusters identified.

Of the 179 ASD subjects, 102 were classified into cluster 1 and 77 into cluster 2. The proportion of subjects from each data source in the two clusters were similar to each other (55% to cluster 1 from clinical trial data and 60% to cluster 1 from research site data). Subjects from the research site (Mean age = 26 years) were slightly older compared to subjects from clinical trial (mean age = 16 years), but there was no difference in the age between the two clusters. Cluster 1 mean domain scores were significantly higher ($P < 0.05$) than that of cluster 2 for all domains. SRS scores were significantly lower ($P < 0.05$) in cluster 2 (mean SRS = 68) compared to cluster 1 (mean SRS = 80). There were no significant differences between the clusters in the other scales ($P > 0.05$).

Conclusions: Unsupervised clustering identified two clusters based on 5 ABI domain scores, ABI core and age. The clustering was along the higher and lower scores of all domains. Visual assessment of the cluster tendency identified additional potential clusters, but the sample sizes limited meaningful exploration. These preliminary exploratory analyses indicate that ABI has the

potential to subtype ASD patients. Confirmatory data are needed from an independent sample to substantiate these findings, including subjects with more severe autism.

Keywords: Autism, Autism Behavior Inventory, ASD Core Symptoms

Disclosure: Nothing to disclose.

T76. It's Not Fair - Persistence and Reward Sensitivity Modulate Reward Omission Response in Adolescents but Not Adults

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Background: Adolescence is a critical period for personality formation, and brain reward circuits are thought to take on a key role in that process toward developing adult goals and behaviors. Little is known, however, how temperament and reward learning relate to foster normal development or create vulnerabilities for maladaptive behavior. We studied brain reward function in adolescents and adults to identify temperamental traits that may be specifically important for adolescent behavior adaptation.

Methods: We recruited from the community 29 healthy adolescent girls and 41 healthy young adult women. Participants completed the Revised Sensitivity to Punishment and Reward Questionnaire, State-Trait Anxiety Inventory (Spielberger, 1983), and the Temperament and Character Inventory (TCI). Brain imaging was performed between 0800 and 0900 hours on a 3T GE Signa scanner (three-plane scout scan 16 seconds) for sagittally acquired, spoiled gradient sequence T1-weighted, 172 slices, thickness = 1mm, TI = 450ms, TR = 8ms, TE = 4ms, flip angle = 12°, FOV = 22cm, scan matrix = 64 × 64, and T2*-weighted echo-planar scans for blood-oxygen-level-dependent (BOLD) functional activity (3.4 × 3.4 × 2.6mm voxels, TR = 2100ms, TE = 30ms, flip angle = 70°, 28 axial slices, thickness=2.6mm, gap = 1.4mm). Taste Reward Task (O'Doherty et al., 2003). Participants learned to associate three unconditioned taste stimuli (US: 1 M sucrose solution, no solution, or artificial saliva) with paired conditioned visual stimuli (CS). Each CS was probabilistically associated with its US such that 20% of sucrose and no solution CS trials were unexpectedly followed by no solution and sucrose US, respectively. We extracted for the prediction error analysis parameter estimates, and for the condition analysis beta values from 18 predefined regions of interest bilaterally (http://marsbar.sourceforge.net/, automated anatomical labeling Atlas, AAL. All data were tested for normality with the Shapiro-Wilk test and Z-transformed when non-normally distributed.

Results: Brain activation Group Contrasts. Unexpected Sucrose Omission, Beta Values. The adolescent group showed a more negative response in almost all regions tested, except for the left superior and the bilateral medial OFC, posterior CC, caudate head, nucleus accumbens, and left substantia nigra. ($p < 0.05$, multiple comparisons corrected).

Unexpected Sucrose Omission Behavior Regression.

Adolescents versus Adults differed for: persistence and bilateral superior FC (R: $z = -2.345$, $p = 0.010$; L: $z = -2.161$, $p = 0.015$), superior medial FC (R: $z = -2.422$, $p = 0.008$; L: $z = -2.194$, $p = 0.014$), middle FC (R: $z = -2.729$, $p = 0.003$; L: $z = -2.438$, $p = 0.007$), superior OFC (R: $z = -2.938$, $p = 0.001$; L: $z = -2.780$, $p = 0.003$), middle OFC (R: $z = -2.594$, $p = 0.005$; L: $z = -2.593$, $p = 0.005$), medial OFC (R: $z = -2.165$, $p = 0.015$, L: $z = -2.990$, $p = 0.001$), inferior OFC (R: $z = -3.013$, $p = 0.001$, L: $z = -3.069$, $p = 0.001$), right anterior cingulate ($z = -2.961$, $p = 0.002$), right ventral anterior insula ($z = -2.190$, $p = 0.014$), bilateral caudate head (R: $z = -2.799$, $p = 0.003$, L: $z = -2.622$, $p = 0.004$), putamen (R: $z = -2.011$, $p = 0.022$; L: $z = -2.439$, $p = 0.007$), ventral striatum (R: $z = -2.082$, $p = 0.019$; L: $z = -2.914$, $p = 0.002$), left nucleus accumbens ($z = -2.584$, $p = 0.005$), and for sensitivity to reward and left inferior OFC ($z = -1.949$, $p = 0.026$), bilateral middle cingulum (R: $z = -2.455$, $p = 0.007$; L: $z = -2.433$, $p = 0.007$), left posterior insula ($z = -1.764$, $p = 0.039$), bilateral caudate head (R: $z = -1.957$, $p = 0.025$; L: $z = -2.041$, $p = 0.021$), left putamen ($z = -1.768$, $p = 0.038$), and bilateral substantia nigra (R: $z = -1.694$, $p = 0.045$; L: $z = -2.022$, $p = 0.022$).

Brain Network Analysis for Associated ROI Activation.

Unexpected Sucrose Omission, Beta Values Regional Correlation Maps: Both groups showed significant within region correlation clusters for FC, CC and insula and striatum, as well as correlations between FC and CC; adolescents, but not adults, showed correlation clusters between FC and insula and striatum and between OFC and FC, anterior CC, insula and putamen and ventral striatum (all $p < 0.000008$, $p < 0.01$ Bonferroni corrected). Unexpected Sucrose Omission Adjusted for Persistence and Sensitivity to Reward, Beta Values Regional Correlation Maps : After adjusting for persistence, the large clusters of correlation between FC, OFC, CC, insular and striatal regions in adolescents largely disappeared. Additional adjusting for sensitivity to reward did not change the pattern. Adjusting for reward sensitivity before adjusting for persistence did not eliminate those correlations.

Conclusions: This study provides new information on brain reward response across age groups and highlights the importance of persistence as a temperamental trait in adolescent development. We propose that persistence is a stable trait that especially during adolescence moderates dopamine-related brain reward response to unexpected omission. This affects a circular process of immediate learning and for adaptation of brain response, followed by adjustments in situation appraisal toward developing new goals and behavior patterns. Over time, when transitioning from adolescence to adulthood, life goals shift and new associations form between temperament and brain response. Those contingencies between temperamental trait and neurobiology may become key elements of understanding learning in the normal transition from adolescence to adulthood as well as for understanding vulnerability for psychiatric illness.

Keywords: Brain Imaging, fMRI, Reward, Adolescence, Personality, Developmental

Disclosure: Nothing to disclose.

T77. Contributions of Prenatal Air Pollution Exposure to the Effects of Early Life Stress on Hippocampal Subregional Volumes and Associations With Perceptual Reasoning

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Background: Both early life stress (ELS) and prenatal exposure to polycyclic aromatic hydrocarbons (PAH), a component of air pollution, are linked to adverse psychiatric outcomes. We have shown that prenatal exposure to PAH moderates the effects of ELS on childhood attention problems. Prior animal and human studies link both attention problems and ELS with reduced hippocampal volumes, and specifically in the CA3. Further, hippocampal volume has been associated with perceptual reasoning. Herein, we investigate if prenatal exposure to PAH moderates effects of ELS on hippocampal volume and whether these effects are associated with perceptual reasoning.

Methods: Thirty-seven African American and Dominican children (7-9 years old) were recruited from a longitudinal birth cohort. Prenatal exposure to airborne PAH was measured during

the third trimester of pregnancy. Mothers reported perceived stress at child age 5. At age 7–9, children completed the Wechsler Abbreviated Scale of Intelligence-2nd edition. The Performance Intelligence Quotient (PIQ) is used as a measure of perceptual reasoning. Bilateral CA1, CA3, and CA4/dentate gyrus hippocampal subfield volumes were extracted using Freesurfer 6.0. First, linear regression tested the effects of PAH, ELS, and their interaction on hippocampal subfield volumes, residualized for age, sex, and total intracranial volume. False discovery rate (FDR) correction was used to adjust for multiple comparisons ($N = 37$). Second, we tested whether hippocampal regions predicted by the interaction of ELS and prenatal air pollution were associated with perceptual reasoning as measured by PIQ ($N = 35$).

Results: Prenatal PAH exposure moderated the effects of maternal perceived stress on right hippocampal subfields, with the strongest effect in the CA3 (pFDR=.04). Children with higher prenatal PAH exposure and higher levels of maternal stress had the smallest right hippocampal subfield volumes. Additionally, right CA3 volume was positively associated with PIQ ($p = 0.03$).

Conclusions: We extend prior findings that prenatal PAH exposure moderates the effects of ELS on child behavior to now include the effects on hippocampal subfield volumes and specifically the right CA3. Further we show that altered hippocampal volume associated with a measure of perceptual reasoning, a capacity that contributes to children's social and academic functioning. Such findings demonstrate the interactive, deleterious effects of early life stress and prenatal air pollution exposure. Furthermore, findings underscore a need to study how mixtures of chemical and social exposures influence neurodevelopment.

Keywords: Hippocampal Subfields, Air Pollution, Perceptual Reasoning, Early Life Stress

Disclosure: Nothing to disclose.

T78. Complex Connectivity in Context: Extrinsic Network Interactions Subserving Differential Socioemotional Task Demands in Adolescents With Autism Spectrum Disorder (ASD)

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Background: Socioemotional deficits play a central role in the Autism Spectrum Disorder (ASD) phenotype and converging evidence suggests that individuals with ASD exhibit atypical neural processing of affective stimuli. Surprisingly, only a handful of studies have used task-based functional connectivity magnetic resonance imaging (fcMRI) to examine brain regions implicated in emotional face processing, particularly during the critical neurodevelopmental period of adolescence. Most fcMRI studies using facial affect stimuli have reported decreased connectivity in adults with ASD compared to typically-developing (TD) controls, although some have shown mixed results. Further, although incongruities have been noted in many widely-used task designs, investigators have continued to incorporate these well-established paradigms because they reliably activate neural circuits of interest.

We thus propose shifting our analysis and interpretation of these existing tasks in an effort to augment our understanding of the neural underpinnings of social deficits in ASD. By examining functional connectivity during an entire task run of conventional emotional face tasks rather than "subtracting" activity from putative control conditions, we may more closely approximate real-world, non-focal experiences of socially-relevant stimuli. Consequently, we may be afforded insight into how individuals with ASD and TD controls differ in their neural response to cognitive and social demands more broadly. We hypothesize that direct between-group comparisons (ASD vs. TD) will reveal extrinsic functional connectivity differences associated with ASD-related characteristics.

Methods: Using a Siemens TIM Trio 3T scanner (Erlangen, Germany) with a 32-channel head coil, we collected task-based fcMRI data from 34 males with and without ASD diagnoses. Exclusion criteria were: IQ ≤ 70, known genetic syndromes related to developmental delays, known or suspected brain malformation, metabolic disorders, CNS infections, vision, hearing or motor impairments, and MRI incompatibilities. Potential TD controls were excluded if they had a history of special education or developmental delay. Ten participants (6 ASD, Mean Age = 13.6 ± 2.4; 4 TD, Mean Age = 14.0 ± 2.8) were excluded from analysis due to excessive head motion in the scanner. Our final dataset included 24 males (Ages 10-18 years): individuals with ASD ($N = 11$; Mean Age: 14.5 ± 3.3 years) and age-matched individuals without ASD ($N = 13$; Mean Age: 14.9 ± 2.2 years).

We selected two commonly-used paradigms in affective science that present static images from a standardized, grayscale stimulus set; all participants completed an emotional face-viewing task and an emotional face-matching task (6 minutes 28 seconds each). Beyond consistently eliciting hemodynamic activity in brain regions subserving processing of facial affect, these two tasks present divergent demands. The face-viewing task requires passive viewing of adult fearful faces, happy faces, and fixation (+) blocks. To ensure attention, participants are asked to press a button when they see an "o" instead of a "+" during the fixation blocks. The face-matching task requires participants to match emotions in adult angry and fearful faces or shapes in horizontal and vertical ellipses and respond with a button press.

To investigate the clinical meaning of group differences in amygdala (AMG) and fusiform gyrus (FG) connectivity, we assessed correlations between scores on the Social Communication Questionnaire (SCQ) with regions of group difference and examined functional connectivity from these socioemotionally relevant regions of interest (ROIs).

Results: Direct between-group comparisons revealed significant differences ($p < 0.01$) in ASD and TD neural response to both tasks but not on measures of task accuracy or reaction times. For the emotional face-viewing task, individuals with ASD demonstrated greater functional connectivity relative to TD controls for both AMG and FG seeds, primarily in regions involved in the Default Mode Network (DMN) and Fronto-Parietal Task Control Network (FPN). While performing the emotional-face matching task, individuals with ASD showed reduced functional connectivity relative to TD controls for both AMG and FG seeds, mainly in regions associated with the Salience Network (SN), Dorsal Attention Network (DAN), and Somatosensory Networks (SMN). Multiple linear regression analyses showed significantly positive correlations between SCQ scores and regions with group differences on the emotional face-viewing task and negative correlations between SCQ scores with regions identified for the emotional face-matching task ($p < 0.05$).

Conclusions: Our findings demonstrate atypical, task-dependent integration of neural circuitry between adolescents with ASD and TD controls despite comparable performance on both tasks. These distinct patterns of functional connectivity also correlate significantly with clinical measures of ASD traits. Results will be discussed in terms of the differential demands posed by each task, the ecological validity of behavioral tasks broadly, and contextually-relevant processing of socioemotional stimuli. Additionally, we will propose potential compensatory strategies used by high-functioning individuals with ASDs as they work to navigate a complex, social world.

Keywords: fMRI Functional Connectivity, Autism Spectrum Disorder, Facial Emotional Processing, Task-Based Functional Connectivity, Social Communication

Disclosure: NIH, Roche: Grant (Self); Roche, Fraser Community Clinics, Minnesota Independence College & Community: Advisory Board, (Self)

T79. Sex Differences in Mild TBI, Internalizing, and Externalizing Behaviors in a Large-Scale Population Study of Youth

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Background: Mild traumatic brain injury (mTBI) accounts for over 85% of TBI diagnoses in children (Rivara, Koepsell et al. 2011) and is associated with long-term adverse events including depression, anxiety, and reduced cognitive functioning, creating significant public health concern (Babikian, Merkley et al. 2015). Research has shown that sex differences in TBI are significant, as males represent the majority of TBI cases across ages, and age-adjusted TBI-related hospitalization rates for males are consistently higher than for females (Coronado, Haileyesus et al. 2015). Despite the prevalence of TBI in males compared to females and the importance of understanding factors related to TBI outcome, limited research has examined the interaction between TBI and clinical symptoms by sex in youth. This study examined internalizing, externalizing, and problem behaviors in children with and without mTBI to determine whether there was a significant difference in clinical profiles of children with a history of mTBI by sex.

Methods: The sample included 10,544 nine- and ten-year-old children from the Adolescent Brain Cognitive Development℠ Study (ABCD Study®). Parents completed a variety of measures including the Child Behavior Checklist (CBCL) and Modified Ohio State University TBI Screen-Short Version (OSU-TBI). CBCL scores on the Withdrawn, Anxious/Depressed, and Somatic Complaints syndrome scales were combined to create an Internalizing summary score, whereas scores on the Aggressive and Delinquent syndrome scales were combined for the Externalizing summary score. These scores were combined with the remaining syndrome scales (Social, Thought, Attention, and Other) to create a Total Problems score. Participant mTBI status was classified as 1) no TBI if they had negative responses to all head injury questions or response to head injury was 'yes' but responses to Loss of Consciousness (LOC) and memory loss were "no" 2) mTBI-LOC if they endorsed TBI without LOC but with memory loss and 3) mTBI +LOC if they reported TBI with LOC less than/equal to 30 minutes. Generalized additive mixed models (GAMMs) were run to examine the association between TBI and parent-reported CBCL scores with age, sex, race, ethnicity, and parental socioeconomic status (SES) included as covariates.

Results: Participants had a mean age of 9.9 years. The sample included 5,058 girls (48%) and 5,486 boys (52%). There were 10,142 participants who reported no TBI, 285 with mTBI without LOC and 117 who endorsed mTBI with LOC in their lifetime. Seven participants who met criteria for lifetime moderate or severe TBI were excluded from analyses due to the small sample size. Boys had a higher incidence of mTBI with and without LOC than girls after controlling for other sociodemographic variables ($p = 0.01$; girls mTBI-LOC = 111, boys mTBI-LOC = 174, girls with mTBI+LOC = 46, boys with mTBI+LOC = 71). Significant associations were seen between mTBI and CBCL scores such that participants with a lifetime history of mTBI-LOC and mTBI+LOC had higher Internalizing (Cohen's d = 0.39), Externalizing (Cohen's d = 0.31), and Total Problems (Cohen's d = 0.40) CBCL scores compared to youth without mTBI ($p < 0.0001$). There was also a main effect of sex with boys demonstrating higher Internalizing (Cohen's d = 0.18), Externalizing (Cohen's d = 0.15), and Total Problem CBCL scores (Cohen's d = 0.19) when compared to girls ($p < 0.0001$). There was no significant interaction between sex and diagnosis (internalizing: F = 1.6, $p = 0.21$; externalizing: F = 0,11, $p = 0.89$; total: F = 0.48, $p = 0.62$).

Conclusions: Overall, our study revealed that in this large sample of youth between 9 and 10 years old, boys were more likely to have a history of mTBI and had higher internalizing and externalizing problems compared to girls. Internalizing and externalizing scores were associated with a history of mTBI. However, there was no TBI by sex interaction, suggesting that the higher CBCL scores associated with mTBI were not dependent on sex. The current study is cross sectional and cannot address whether externalizing or internalizing behaviors play a causal role in mTBI. Given reports from other studies that boys have worse outcomes after TBI such as depressive and anxious symptoms, somatic concerns, attention difficulties, defiant behavior and aggression, our findings highlight the need for not only prevention but also for early clinical interventions even when the TBI is considered mild. The higher incidence of mTBI in boys and evidence that boys often have worse trajectories post-TBI suggest that early interventions should be targeted to boys and focus on treatment of both internalizing and externalizing behaviors.

Keywords: TBI, Sex Differences, Children, Internalizing Behavior, Externalizing Behavior

Disclosure: Nothing to disclose.

T80. ERP Task Reveals Potential Compensatory Neural Mechanisms Aiding Cognitive Flexibility in Fragile X Syndrome

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Background: Cognitive flexibility is highly impaired in Fragile X Syndrome (FXS), the most common inherited intellectual disability and monogenic cause of autism spectrum disorder. This is seen in resistance to change in routines and increased anxiety when a preferred response is prevented. The alterations in neural processes underlying these deficits remain unclear, limiting advances in mechanistic understanding and treatment development.

Methods: Sixteen participants with full-mutation FXS (7 males, 15-45 years) and 15 typically-developing controls (TDC; age- and sex-matched) completed a spatial reversal learning paradigm during continuous EEG recording using a 128-channel EGI system. Participants were instructed to select the box in the correct location, with correct location changing following 3-5 consecutive correct responses. Data were epoched from -500 to 800ms with respect to the onset of response feedback, as indicated by a coin (correct) or red 'X' (incorrect). We examined fronto-parietal event-related potentials (ERPs) following feedback onset: N1, P3a, and P3b. ERPs were defined as the minimum or maximum amplitudes in a time window centered on the grand average peak amplitude +/− 50ms. Average peak amplitude and peak latency were calculated for each participant. Exploratory clinical associations also were examined.

Results: Fronto-central N1 and P3a amplitudes were increased, and central-parietal P3b amplitudes and latencies were increased in FXS compared to TDC. Amplitude elevations in FXS were present regardless of feedback type and remained significant after controlling for IQ. Elevated P3a and P3b amplitudes were related to fewer flexibility errors and less severe parent-rated repetitive and anxious behaviors.

Conclusions: Separately examining fronto-central and central-parietal clusters, we demonstrated atypical amplitude and timing of ERPs in individuals with FXS during a reversal learning EEG task,

providing novel evidence of frontoparietal network functioning related to cognitive flexibility deficits in FXS. Individuals with FXS demonstrated increased amplitudes following behavioral feedback for both P3 components as well as for N1. These findings suggests hyper-responsiveness to visual feedback stimuli (N1, P3a), consistent with studies examining evoked responses to sensory stimuli, and increased cognitive effort (P3a, Pb3) necessary for completing a relatively simple cognitive task. Exaggerated P3 amplitudes of ERPs in individuals with FXS were related to fewer errors and less severe clinical features, suggesting increased amplitudes of ERPs in FXS participants may actually represent compensatory neural mechanisms to support flexible behavior among some individuals. Together, our findings provide novel insight into a critically under-studied domain of behavioral problems in FXS and their neurophysiological mechanisms.

Keywords: Fragile X Syndrome, Event-Related Potentials, Cognitive Flexibility, Cognitive Neuroscience, Reversal Learning

Disclosure: Nothing to disclose.

T81. A Computationally-Identifiable Dimensional Structure in Neonatal Social Communication Predicts Post-Pubertal Social Behaviors in a Mouse Model of 16p11.2 Deletion

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Background: The variable developmental trajectories among carriers of copy number variants (CNVs) remain a major challenge for early and precise diagnoses. An objective and quantitative method of predicting the developmental trajectories of infants early in life is needed for two reasons. First, a better understanding of the variable developmental trajectories would provide mechanistic insights into developmental neuropsychiatric disorders associated with CNVs. Second, because some forms of early intervention improve the prognoses of ASD, identification of genuine early signs are essential to avoid false positive and false negative signs. Carriers of hemizygous deletion at human chromosome 16p11.2 exhibit autism spectrum disorder (ASD), other developmental neuropsychiatric disorders and atypical motor, social, and cognitive developmental trajectories at elevated rates. However, there are many cases of apparently "normal" or inconsistent phenotypes in mouse models of 16p11.2 deletion. We independently developed a coisogenic model of 16p11.2 deletion and prospectively applied deep-phenotyping and computational data mining to identify quantitative variables in neonatal social communication that predict later behavioral abnormalities and determine the degree of predictability of neonatal dimensions of social communication for post-pubertal social behaviors.

Methods: We developed a coisogenic mouse model of human 16p11.2 hemizygous deletion through in vitro Cre-mediated recombination of a 378 kb region of the 7qF3 region spanning from Mapk3 to Spn genes, a mouse region homologous to the human 16p11.2 locus, and applied computational approaches to identify dimensions in neonatal social communication that have predictive power for post-pubertal social behaviors in a co-isogenic mouse model of human 16p11.2 hemizygous deletion (Del/+) and their wild-type littermates (+/+). ES cells derived from C57BL/6N were used for gene targeting and the same inbred mouse was used for breeding. Male mice were tested prospectively for vocalization induced by a brief maternal separation at the neonatal stage (P8 and P12, +/+, $n = 29$; Del/+, $n = 15$), and subsequently, mice survived to 1 month of age were tested for behaviors relevant to developmental neuropsychiatric (+/+, $n =$ 14-20; Del/+, $n =$ 8-9). To identify neonatal dimensions that predict later social behaviors, we applied machine learning and other computational data mining. Variables of neonatal vocalizations were selected by least absolute shrinkage and selection operator (Lasso) and Markov model, and regression models were constructed to predict post-pubertal social behaviors. We compared the Statistical Analyses Group means using analysis of variance (ANOVA), Newman-Keuls post-hoc tests, or two-sided *t*-tests when there were only two groups. A probability of < 0.05 was considered significant. When multiple tests were applied to a dataset, the significance level was adjusted using Benjamini-Hochberg's correction. When homogeneity of variance or normality was violated, Wilcoxon non-parametric tests were used.

Results: RNA-seq analysis confirmed that the expression of genes encoded in the deleted region was significantly reduced in Del/+ mice, compared to +/+ mice ($p < 0.05$).

Neonatal Del/+ and +/+ littermates were indistinguishable at P8 and P12 in the average numbers of each call type and in all calls. At 1 month of age, Del/+ mice were indistinguishable from +/+ littermates in reciprocal social interaction ($P > 0.05$). However, Del/+ mice exhibited fewer olfactory responses and less habituation to a social odorant (i.e., urine smell of another mouse), compared to +/+ mice at 1 month of age ($p = 0.001$).

Lasso determined that two-call sequences from Frequency steps to Flat and from Complex to Upward best predicted post-pubertal reciprocal social interaction in +/+ mice ($p = 0.012$ to $p = 9.8 \times 10^{-5}$ for model fitness of all predictive models). The best predictors for the time mice spent in sniffing another mouse's urine were the ratio of Complex in +/+ mice, and the probability of transition from Ambiguous to Downward in Del/+ mice ($p = 0.0052$ to $p = 3.1 \times 10^{-5}$ for model fitness).

Markov models identified frequently used neonatal call-sequences that were correlated with social behaviors. Frequent steps to Flat, Hump to Downward, and Two-syllable to Flat were correlated with reciprocal social interaction in +/+ ($p = 0.0079$ to $p = 9.8 \times 10^{-5}$ for model fitness); Flat to Flat and Complex to Flat were predictors for Del/+($p = 0.012$ to $p = 0.0019$ for model fitness). Hump to Downward was correlated with an olfactory response to a social cue in both +/+ and Del/+ ($p = 0.022$ to $p = 5.7 \times 10^{-5}$ for model fitness).

Conclusions: We developed predictive models from neonatal social communication for reciprocal social interaction and olfactory response to a social cue in a mouse model of 16p11.2 deletion, based on a) all independent variables including call features and genotype by Lasso regression models and b) frequently emitted two-call sequences by Markov models. These approaches collectively generated predictive paths from neonatal social communication to post-pubertal social behaviors.

Keywords: CNV, 16p11.2, ASD, Developmental Neuropsychiatric Disorders, Mouse

Disclosure: Nothing to disclose.

T82. Modeling Generational Consequences of the Perceived Stress of Racism on Maternal-Infant Health Outcomes

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Background: Despite major advancements in maternal-fetal health, African-American women and their infants are three times more likely to die in childbirth or postpartum than their

non-Hispanic white counterparts, independent of education and income. A known contributing factor pervasive across socioeconomic status is the stress of racism. Cumulative racial discrimination experienced across the lifespan precipitates a state of chronic stress, termed allostatic load or "weathering". This increase in allostatic load is supported by blunted circadian cortisol rhythms, impaired stress responses, and increased risk of chronic and inflammatory diseases in African American women. Lifetime adversity experience prior to conception is also a strong predictor of adverse perinatal outcomes and offspring neurodevelopmental disorders. As pregnancy is a time of incredible metabolic demand, increased allostatic load prior to pregnancy may contribute to changes in the maternal milieu that affect offspring development. However, little is known about the biological mechanisms involved. We have developed a novel mouse model of maternal preconception stress where female, but not male, offspring show dramatic changes in the fetal brain transcriptome and hypersensitivity to stress as adults. We hypothesize that preconception adverse experiences program persistent changes in the maternal milieu that are unmasked by the energetic demands of pregnancy. Here, we examine the programmatic role of preconception maternal experiences on the earliest stages of development, the oocyte and early embryo.

Methods: A subset of African-American women, recruited as a part of a larger study on risk factors of PTSD, were assessed for lifetime trauma history and discrimination experience. Plasma samples from all participants were used to quantify circulating cell-free mitochondrial DNA. Circulating cell-free mitochondrial DNA is a peripheral biomarker of cellular stress, and is positively associated with chronic metabolic, inflammatory, and affective disorder severity and recovery. We evaluated circulating cell-free mitochondrial DNA as a biomarker of the persisting effects of stress in the plasma of African-American women reporting high and low lifetime discrimination experience. To validate our translational mouse model, we also evaluated circulating cell-free mitochondrial DNA from female mice 4 weeks post-chronic stress.

To evaluate the role of the maternal milieu as a mechanism of maternal preconception stress (MPS) programming, adult female mice (Fo) were exposed to chronic stress from 4-10 weeks of age, followed by two weeks to recover from the acute effects of stress, prior to mating. MPS and control females (Fo) were bred, and embryos were transferred into naïve recipient females. The resulting offspring (F1) were followed for growth and assessed as adults for hypothalamic-pituitary-adrenal (HPA) stress axis reactivity.

Results: African-American women who report experiencing high lifetime discrimination had elevated circulating cell-free mitochondrial DNA, supporting previous reports of increased allostatic load. Female mice (Fo) exposed to our chronic stress paradigm also increased circulating cell free mitochondrial DNA four weeks after the cessation of stress, consistent with human data and indicating a persistent effect of previous stress experience. Changes in offspring (F1) placental and fetal brain transcription suggest long-lasting sex-specific programming. Therefore, embryos from MPS and control females were transferred into naïve recipient dams and tested for stress-responses in adulthood, allowing us to dissect persistent MPS effects on the maternal milieu (F0) from embryonic programming (F1) in driving sex-specific changes in offspring neurodevelopment.

Conclusions: These studies support the role of circulating cell-free mitochondrial DNA as a persistent biomarker of lifetime adversity in humans and chronic stress in mice. These results also highlight the importance of maternal (F0) preconception adverse experiences on female offspring (F1) specific neurodevelopment. Taken together, these data suggest a generational effect of cumulative adverse experiences including racism stress, through heightened stress responses in female offspring (F1), perpetuating programmatic changes to the stress axis in females and increasing risk across subsequent generations (Fn).

Keywords: Lifetime Stress, Stress and Trauma, Circulating Mitochondrial DNA, Developmental Trajectory, Health Disparities

Disclosure: Nothing to disclose.

T83. A Nonhuman Primate Model of Human Non-Suicidal Self-Injury: Serotonin-Transporter Genotype-Mediated Typologies

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Background: While non-suicidal self-injury (NSSI) occurs in the general population at a surprisingly high rate, with higher rates among certain clinical diagnoses, its etiology is not well-understood. Consequently, the DSM-5 lists NSSI as requiring further research. This study utilizes a rhesus macaque model to assesses the role of early adverse experiences and variation in the serotonin transporter genotype (5-HTT) in the etiology of NSSI.

Methods: Subjects ($N = 161$) were reared in one of three conditions (mother-reared (MR), peer-reared (PR), or surrogate peer-reared (SPR)), and classified as NSSI ($n = 18$) or non-NSSI ($n = 143$). Subjects were genotyped for the 5-HTT genotype and their behaviors were recorded during an ecologically-meaningful, stress-evoking, intruder challenge paradigm. At the end of the paradigm, blood samples were obtained and assayed for concentrations of plasma cortisol and adrenocorticotropic hormone (ACTH).

Results: NSSI subjects were more likely to be SPR, than MR or PR, paralleling human studies showing that individuals that exhibit NSSI tend to have experienced early life abuse or neglect. Results also indicated that variation in the 5-HTT genotype differentiated the NSSI-afflicted subjects. NSSI subjects that were homozygous for the L allele exhibited high plasma ACTH and high rates of stress-induced stereotypies; whereas NSSI subjects with the s allele exhibited impulsive behaviors, including frequently approaching the potentially dangerous intruder, high rates of aggressive vocal threats, and more activity.

Conclusions: These results suggest that there may be different 5-HTT genotype-mediated NSSI typologies, and that early experiences and variation in the 5-HTT genotype may be important factors in understanding the etiology of NSSI.

Keywords: Non-Suicidal Self-injury (NSSI), Serotonin Transporter Genotype, Nonhuman Primate Model, Impulsivity, Early Rearing

Disclosure: Nothing to disclose.

T84. Altered Neural Response to Novel Social Stimuli in Behaviorally Inhibited Preschool Children

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Background: Behavioral inhibition (BI), a common temperament trait characterized by inhibited behavior in response to new stimuli, is associated with a sevenfold risk for social anxiety disorder in adolescence and adulthood. Behavioral work has identified social flexibility, the ability to flexibly attend to new information in social contexts and update one's goal-directed behavior in response, as a core deficit that may influence anxiety trajectories. Little to no work has evaluated neural correlates of

social flexibility in very young BI children. Understanding the nature of neural deficits at this age could aid clinicians in creating developmentally sensitive interventions that target this circuitry. The aim of this study was to delineate the neural circuitry underlying social flexibility in BI children, using an ecologically valid task and non-invasive imaging methods. The ventrolateral prefrontal cortex (vlPFC) is involved in flexibly updating goal-directed behavior and is part of a ventral attention network junction which is involved in orienting toward new stimuli. Some work has implicated diminished activity in the vlPFC in BI and social anxiety in adolescents. Capturing neural patterns during the preschool period in which BI traits are first observable and stabilizing will allow us to uncover neural alterations associated with this early trait. Encouraging BI children to engage in new social experiences (i.e., via exposures) could elicit changes in circuitry involved in social flexibility, thereby allowing children to update social information in the environment (i.e., recognize unfamiliar child is smiling). Increased function in social flexibility regions could help remove uncertainty from social environments, reduce vigilance, and aid in greater approach to new stimuli. Indeed, vlPFC activation has been shown to increase following cognitive behavioral therapy (CBT), although the mechanism involved is still unknown. The use of near-infrared spectroscopy (NIRS), a non-restrictive child-friendly optical imaging method that allows for naturalistic social interaction, during in vivo exposures could elucidate how changes in vlPFC with CBT occur. We hypothesized that 3- to 5-year old children high on BI would show lower activity in regions implicated in social flexibility, specifically the ventrolateral prefrontal cortex.

Methods: Participants were 48 3- to 5-year old preschool children, 23 with high levels of behavioral inhibition (BI) and 25 with low levels of behavioral inhibition (BN) based on parent-report on the Behavioral Inhibition Questionnaire (BIQ). Of these 48 children, 50% were girls. Children and parents participated in a laboratory visit for near-infrared spectroscopy (NIRS) while children completed the Playdate task, a previously validated task in which participants selected children for a future playdate from images of unfamiliar, age-matched peers (see Howarth et al., 2013). Children then received feedback about which peers chose to have a playdate with them in the future. Feedback thus fell into one of four conditions—interested/accepted, not-interested/accepted, interested/not-accepted, and not-interested/not-accepted. Prior work has demonstrated that higher levels of behavioral inhibition was associated with greater emotional distress to the not-interested/accepted condition (i.e., being picked for a playdate by a peer that the target participant did not like). Parents also reported on child anxiety using the Preschool Anxiety Scale.

Results: BI and BN children did not differ on age, sex, or presence of parent anxiety disorders. BI children had higher scores on the Preschool Anxiety Scale (PAS) relative to BN children (MBI= 24.04, MBN = 5.39, F = 75.62, $p < 0.001$). As hypothesized, in response to being accepted by a non-liked peer, BI children showed lower neural response in the left and right lateral prefrontal cortex (BA 10) and the right TPJ ($t = -5.01$, pFDR < 0.001; $t = -3.92$, pFDR <0.001, $t = -4.92$, pFDR <0.001 respectively) compared to BN children.

Conclusions: The current study's design mirrors an exposure likely to be implemented during therapy. Specifically, children are asked to plan a playdate with a set of unfamiliar peers, which can be anxiety provoking for behaviorally inhibited children. Findings from the current study can elucidate neural circuitry involved during exposures and how this circuitry is related to concurrent child behavior and changes in behavior over time. Specifically, our findings that BI children show lower activity in regions within the ventral attention network (i.e., vlPFC and TPJ) may suggest that BI children have difficulty flexibly attending to new information in social contexts (new peer is smiling and looks friendly) and updating goal-directed behavior in response (wanting to play with this new peer in spite of initial impression). Thus, this neural pattern may reinforce emotional distress and avoidance rather than promoting social approach. If replicated, interventions that target these neural regions may be helpful for promoting socially flexible behavior in novel situations.

Keywords: Anxiety, Social Behavior, Temperament

Disclosure: Nothing to disclose.

T85. Stress Impacts Corticoamygdalar Connectivity in an Age-Dependent Manner

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Background: Stress is a socio-environmental risk factor for the development of psychiatric disorders with the age of exposure potentially determining the later outcome. Several brain regions mediate stress responsivity, with a prominent role of the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA) and their reciprocal inhibitory connectivity. Here we investigated the impact of stress exposure during adolescence and adulthood on the activity of putative pyramidal neurons in the BLA and corticoamygdalar plasticity using in vivo electrophysiology.

Methods: 155 male Sprague-Dawley rats were subjected to a combination of footshock/restraint stress in either adolescence (postnatal day 31-40) or adulthood (postnatal day 67-76). In vivo extracellular recordings of spontaneously active putative pyramidal neurons in the BLA and plasticity recordings of the BLA-mPFC/mPFC-BLA pathway were performed after 1-2 and 5-6 weeks of either adolescent and adult stress. Different animals were used for spontaneous BLA pyramidal neuron activity and plasticity recordings. All procedures were carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh.

Results: Both adolescent and adult stress increased the number of spontaneously active putative BLA pyramidal neurons 1-2 weeks (2-way ANOVA, $p < 0.05$ for condition, $n = 5$-6), but not 5-6 weeks post-stress (2-way ANOVA, p>0.05). No changes were found in the firing rate of the cells recorded in both time-points after adolescent and adult stress (2-way ANOVA, $p > 0.05$). High-frequency stimulation (HFS) of BLA and mPFC depressed evoked spike probability in the mPFC and BLA, respectively, in adult (2-way ANOVA, $p < 0.05$ for time, $n = 6$-7) but not adolescent rats (2-way ANOVA, $p > 0.05$ for time, $n = 6$-7). In contrast, an adult-like BLA HFS-induced decrease in spike probability of mPFC neurons was found 1-2 weeks post-adolescent stress (2-way ANOVA, $p < 0.05$ for condition, time, and interaction, $n = 6$-8). At adulthood, impairments in mPFC and BLA neuron discharge were found 1-2 weeks post-stress after BLA and mPFC HFS (2-way ANOVA, $p < 0.05$ for time, condition, and interaction, $n = 6$-9), respectively. No change was found 5-6 weeks post-adolescent or adult stress (2-way ANOVA, $p > 0.05$ for condition, $n = 6$-9).

Conclusions: Our findings indicate that stress during adolescence may accelerate the development of BLA-PFC plasticity, probably due to BLA hyperactivity, which can also disrupt the reciprocal communication of BLA-mPFC after adult stress. Therefore, precocious BLA-mPFC connectivity alterations may represent an early adaptive stress response that ultimately may contribute to vulnerability to adult psychiatric disorders.

Keywords: Chronic Stress, Adolescence, Basolateral Amygdala, Medial Prefrontal Cortex

Disclosure: Nothing to disclose.

T86. Sensory Mechanisms of Motor Variability and Regularity in Autism Spectrum Disorder

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Background: Deficits in sensorimotor integration are highly prevalent in persons with Autism Spectrum Disorders (ASD) and are associated with more severe core symptoms. Our prior ASD studies of precision manual motor control demonstrate increased variability and regularity that are exacerbated when visual feedback is either enhanced or degraded. These findings suggest individuals with ASD show an over-reliance on visual feedback during basic motor actions. Other studies have indicated individuals with ASD show a heightened reliance on proprioceptive feedback information during motor learning, suggesting separate sensory feedback processes may be selectively altered in ASD. To clarify sensory mechanism of increased motor variability and regularity in ASD, the present study characterized precision manual motor behavior during conditions in which visual or proprioceptive feedback was altered.

Methods: Forty-three participants with ASD (M: 32, F: 11) and 23 controls (M: 11, F: 12), ages 10-20 years, completed tests of precision gripping. Participants were instructed to squeeze on a force sensor with their dominant hand index finger and thumb. During gripping, they viewed a stationary target force bar and a separate force bar that moved up with increased force. They were instructed to press on the force sensors so that the force bar reached the level of the target bar, and then to keep it as steady as possible. Visual feedback was manipulated by changing the visual gain of the force bar across three levels (low, medium, and high). The force bar moved less per change in force output for lower compared to higher gains. To assess the impact of altering proprioceptive feedback, 80 Hz tendon vibration was applied at the wrist to induce a proprioceptive illusion of muscle contraction and compared to a condition with the tendon vibrator turned off. Force variability (standard deviation) and regularity (sample entropy, or SampEn) each were examined using separate multilevel models (MLM) including random slopes for participant, Group, Gain Level, Vibration Frequency, Age, and all 2- and 3-way interactions as predictors.

Results: Individuals showed less change in force variability during tendon vibration compared to TD controls (Group x Tendon Vibrator condition: $t = -1.97$, $p = 0.0496$). Individuals with ASD also showed stronger age-associated reductions in force variability relative to controls across tendon vibrator conditions and gain levels (Group x Age: $t = -4.71$, $p < 0.0001$). Individuals with ASD also showed greater age-associated increases in force regularity relative to controls, especially at higher gain levels (Group x Gain Level x Age: $t = -3.22$, $p = 0.0014$). Individuals with ASD showed age-associated increases in regularity across tendon vibrator conditions, but these age-associated gains were only seen in controls during conditions in which proprioceptive feedback was not manipulated (Group x Vibration Frequency x Age: $t = 2.46$, $p = 0.0144$).

Conclusions: Our findings indicate that while controls integrate both proprioceptive and visual feedback information during precision manual motor control, persons with ASD rely primarily on visual feedback and show minimal change in performance when proprioceptive feedback is disrupted. Our results also suggest altered developmental trajectories of sensorimotor processing in individuals with ASD. Control participants show minimal change in motor variability and regularity across our age range while persons with ASD continue to show age-associated gains across adolescence and early adulthood suggesting sensorimotor issues may be more prominent in early development.

Keywords: Sensorimotor, Entropy, Autism Spectrum Disorder and Related Syndromes, Motor Behavior

Disclosure: Nothing to disclose.

T87. Reduced Incentive Salience to Monetary Reward-Related Stimuli in Anorexia Nervosa

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Background: Beside impairment in food reward processing, anorexia nervosa (AN) is also associated with aberrant non-food reward processing manifested as abnormal reward responsiveness, reduced novelty seeking, and lower willingness to pursue hedonic activities. This subject, however, has been underinvestigated in the field of anorexia research. This project explored an important aspect of non-food-related reward processing in AN, motivation to obtain (monetary) reward, from neurobehavioral perspective by using and integrating concepts and methods from affective neuroscience and neuroimaging.

Methods: Fifty-four adolescents (controls: $n = 25$; AN: $n = 29$) were recruited for this study. All participants performed a monetary reward task in the MRI scanner in which they pushed a button after visual cues to potentially obtain a monetary reward. Our primary behavioral outcome measure, response time (RT), was calculated as the duration between the presentation of a visual cues and a button push to initiate the task to obtain the monetary reward. We hypothesized that RT is mediated by activation of the mesolimbic circuit involves in incentive salience: ventral tegmental area/substantia nigra pars compacta (VTA/SNc), and its connectivity with nucleus accumbens (NAcc). Regional activity of VTA/SNc and VTA/SNc-NAcc functional connectivity (tested by Psychophysiological interaction (PPI) method) during RT were measured for all subjects. Neurobehavioral coupling mechanisms underlie incentive salience (motivation) to acquire reward were assessed by measuring the association between RT and VTA/SNc activity or VTA/SNc-NAcc connectivity.

Results: In control subjects, we found neuronal engagement of the motivation circuit during RT period, manifested by increased activity in the ventral tegmental area/substantia nigra pars compacta (VTA/SNc), and its connectivity with nucleus accumbens (NAcc), relative to baseline. Moreover, significant negative correlations were detected between RT duration and the level of activity in VTA/SNc ($p = 0.005$, $r = -0.54$) alongside with a significant negative correlation between RT duration and value of the right VTA/SNc-NAcc functional connectivity in controls. Those with AN showed significantly longer RT compared to controls (AN $= 1.3 \pm 0.1$ s vs controls $= 1.1 \pm 0.1$ s ; $p = 0.04$; controlled for age and puberty score) with significantly lower connectivity between the right VTA/SNc and left NAcc. Unlike healthy controls, no significant correlation was detected between RT duration and VTA/SNc activity level or VTA/SNc-NAcc functional connectivity in those with AN.

Conclusions: Our findings provide behavioral evidence of impaired incentive salience (motivation) to acquire non-food-related reward is in AN. Based on our neuroimaging results, we suggest dysfunction in the motivation circuit (decreased the connectivity between VTA/SNc and NAcc regions) and abnormality in the underlying neurobehavioral coupling as the neurobiological mechanisms of aberrant motivation in AN.

Keywords: Anorexia Nervosa, Monetary Reward, Mesocorticolimbic System, Brain Imaging, fMRI

Disclosure: Nothing to disclose.

T88. Resting-State Internetwork Influence Predicts Treatment Response in Women With Bulimic-Spectrum Eating Disorders

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Background: Difficulty regulating intense, volatile emotion has been consistently implicated in the development and maintenance of binge eating and purging. In addition, some data suggest that severe emotion dysregulation predicts a more chronic course of illness in bulimic-spectrum disorders. However, the neural underpinnings of these emotion-symptom dynamics remain uncharacterized. In the current study, we used Dependency Network Analysis (DEPNA), a graph theoretical approach, to investigate whether interactions between emotion regulation and emotion reactivity circuits can predict treatment response. The method assesses functional relations between networks by quantifying the influence of each brain area in one network over the correlations between all pairs of brain areas in another network. DEPNA has been used to study anxiety, mood, and neurodegenerative disorders, but this is its first application in eating disorders.

Methods: Adult female patients with bulimic-spectrum eating disorders in an intensive dialectical behavior therapy program ($n = 19$) and female healthy controls ($n = 19$) completed an eyes-open resting-state fMRI scan. Patients subsequently completed biweekly surveys throughout treatment. Emotion regulation and reactivity network nodes were selected and categorized based on results of a meta-analytic search in Neurosynth and a theoretical neural model of emotion regulation. For each participant, DEPNA quantified internetwork influences of each regulation node on the entire reactivity network, as well as the total internetwork influences of each network on the other. The total influence of the reactivity network on the regulation network was subtracted from the influence of the regulation network on the reactivity network to generate a relative internetwork influence value. T-tests compared groups on internetwork influences at baseline. Multilevel models were used to identify internetwork influences that modulated the slope of change in symptoms and therapeutic skills use over the course of treatment.

Results: Although no group differences in inter-network influences were statistically significant, stronger relative influences of the regulation network on the reactivity network at baseline predicted larger decreases in purging frequency ($z = 6.31$) and larger increases in therapeutic skills use ($z = 2.98$) over treatment (p'sFDR < 0.05). At the nodal level, stronger influences of ventrolateral prefrontal cortical regulation network nodes on the reactivity network predicted larger decreases in binge eating ($z = -2.01$) and larger decreases in impulsive action in the context of negative emotion ($z = -2.22$; p's < 0.05, uncorrected).

Conclusions: These preliminary findings suggest that individual differences in network organization predict treatment response in bulimic-spectrum disorders. Quantifying the impact of emotion regulation circuits on emotion reactivity circuits may help identify those most and least likely to benefit from existing treatments. Increasing this inter-network influence could also be a mechanistic target for new interventions.

Keywords: Graph Theory, Neural Predictors, Eating Disorders, Emotion Circuitry, Treatment Outcome Prediction

Disclosure: Nothing to disclose.

T89. Fatty Acids and Their Lipogenic Enzymes in Anorexia Nervosa Subtypes

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Background: Fatty acids in the circulation can be influenced by the composition of dietary intake. It is postulated that unhealthy eating behaviors including extreme avoidance of high-fat foods play a key role in fatty acid dysregulation in patients with anorexia nervosa (AN). Eating behavior is notably different between AN patients with the restricting subtype (AN-R) and the bingeing and purging subtype (AN-BP), yet, few studies have directly addressed the effects these differences have on fatty acid signature. In this study, we explored if the pattern of fatty acid dysregulation is differentially observed in each of the AN subtype, and examined the association between fatty acids and lipogenic enzymes with key eating disorder phenotypes including anxiety, which promotes aversion toward high-calorie, high-fat foods and unhealthy dieting practices.

Methods: 26 fatty acids were measured using both fasting and 2-hour postprandial plasma from sex- and age-matched 25 women with AN-R (27.56 ± 8.1 [age mean±SD]), 25 women with AN-BP (32.80 ± 11.44), and 46 healthy control women (30.67 ± 9.33). Fatty acids were quantified using gas chromatography-mass spectrometry whereas phenotype data were collected on the day of the study visit. Fatty acid ratios were used as proxy markers of in vivo lipogenic enzyme activities. Phenotypes assessed were collected using the Beck Depression Inventory, Beck Anxiety Inventory, Food Aversion Questionnaire, and Eating Disorder Inventory. Multivariate analysis of covariance models adjusting for age and BMI were used to compare fatty acids and enzyme activities among AN-R, AN-BP, and control groups. Association and correlation between AN-associated fatty acids and lipogenic enzymes with phenotypes were analyzed using Pearson's correlation and multiple linear regression models adjusted for age and BMI.

Results: None of the individual fatty acids differed significantly between AN-R and AN-BP groups. In the fasting state, saturated lauric acid was marginally higher in AN-BP compared to AN-R (by 76%, $p = 0.05$) and significantly higher than controls (by 138%, $p = 0.042$). Of the n-3 fatty acids, alpha-linoleic acid (ALA) (by 130%, $p < 0.001$), stearidonic acid (by 68%, $p = 0.007$), and docosapentaenoic acid (DPA) (by 70%, $p = 0.007$) were higher in AN-R while eicosapentaenoic acid (EPA) was elevated in both AN-R (by 53%, $p = 0.015$) and AN-BP (by 56%, $p = 0.006$) compared to controls. In the postprandial state, ALA was elevated in AN-R (by 90%, $p < 0.001$) while EPA was higher in AN-BP compared to controls (by 71%, $p = 0.002$). None of the desaturases and elongases differed significantly among AN-R, AN-BP, and control groups.

For AN-BP group, EPA was inversely associated with fasting state anxiety ($r = -0.46$, $p = 0.022$; adjusted $p = 0.038$). Delta-5-desaturase activity was associated with postprandial change in anxiety (adjusted $p = 0.033$) while elongase-6 (ELOVL6) was correlated with illness duration ($r = 0.43$, $p = 0.04$).

For AN-R, EPA was associated with illness duration (adjusted $p = 0.049$) while DPA was correlated with illness duration ($r = 0.50$, $p = 0.015$) and inversely correlated with postprandial change in anxiety ($r = -0.44$, $p = 0.040$). Both Delta-6-desturase (D6D) and stearoyl-CoA-desaturase-18 (SCD18) were associated with fasting-state anxiety (adjusted p-values: $p = 0.041$ and 0.043, respectively) while ELOVL6 was negatively associated with postprandial change in food aversion (adjusted $p = 0.037$).

Depression, fasting state food aversion, and postprandial change in food aversion were not associated with any of the fatty acids in either AN subtypes. AN recovery status and race of the study participants did not affect the associations observed.

Conclusions: Our study yielded insufficient evidence to conclude that AN clinical subtype directly contributes to or modifies the fatty acid dysregulation found in AN. This finding is important because if the hypothesis that diet was the principle cause of lipid dysregulation in AN were true, we should have observed a more significant difference in fatty acid signature between AN-R and AN-BP subtypes. Our results once again shed light on a pronounced lipid alteration in AN that is characterized by an elevation of n-3 fatty acids that are also linked to anxiety. We further concluded that neither extreme restrictive eating commonly found in AN-R nor the addition of binge eating and purging behavior commonly found in AN-BP played a significant role to modify the fatty acid dysregulation in AN. Our data imply that endogenous factors affecting metabolism of fatty acids including genetic susceptibility may contribute to AN lipid dysregulation more significantly than the unhealthy eating behavior. Future research should focus on identification of these endogenous factors to improve quality of life for patients with AN.

Keywords: Fatty Acids, Anorexia Nervosa, Clinical Subtypes

Disclosure: Nothing to disclose.

T90. Vascular Endothelial Growth Factor in Serum Increases in Those Whose Depression Remit After Repetitive Transcranial Magnetic Stimulation but Not in Non-Remitters: Pilot Study

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Background: Major Depressive Disorder (MDD) is a devastating illness that affects more than 300 million people worldwide and an estimated 17.7 million people in the US alone experiences depression annually. Unfortunately, a substantial portion of patients do not respond to medications or psychotherapy. Transcranial magnetic stimulation (TMS) therapy is a relatively novel therapeutic modality effective for those who have failed to respond to pharmacotherapy and psychotherapy, however the mechanism of action behind TMS's antidepressant effect is still being elucidated. Vascular endothelial growth factor (VEGF) is an endothelial mitogen widely expressed in the cerebrovasculature and involved in myriad of functions including angiogenesis and hypothesized to be involved in MDD pathology. Some studies have examined peripheral VEGF as potential biomarkers or a player in MDD treatment, including reports of increased VEGF levels after ECT. Additionally, animal models of some neurological disorders have shown VEGF to be affected by TMS. However, there is no published TMS studies in humans examining VEGF.

Methods: Serum was collected from a naturalistic population of 15 patients (40% male, 60% female) with treatment resistant major depressive disorder (MDD) approved to receive standard TMS therapy, at baseline (prior to receiving first session of TMS) and immediately after the 30th session (henceforth referred to as post or Tx30). VEGF concentration was determined via Enzyme-linked Immunosorbent Assay and all samples were run in duplicates. Inventory of Depressive Symptomatology Self Report was used as a measure of depression symptom severity, clinical response (≥50% improvement) and remission (end score ≤ 14). Mann-Whiney U and Kendall's Tau Correlation were used for continuous variables. Treatment was initiated at standard "on-label" 10 Hz stimulation delivered to the dorsolateral left prefrontal cortex (DLPFC) daily at 120% maximum intensity relative to their motor threshold for a minimum of 3000 pulses.

Results: Mean Vascular Endothelial Growth Factor (VEGF) concentration for the group of 15 participants did not change significantly from baseline to Tx30 overall, however there was evidence that successful treatment with TMS was associated with change in Vascular Endothelial Growth Factor (VEGF). $N = 4$ of the 15 participants met criteria for remission following TMS and $n = 8$ met criteria for response. Amongst patients who remitted, VEGF increased from pre- to post-TMS (mean %change +30.3%) whereas VEGF decreased in nonremitters (mean % change −9.87%) ($p < 0.05$). This same pattern was observed when comparing mean %change in VEGF between responders (+14.7%) and non-responders (−14.9%) ($p = 0.054$). Similarly, a statistically significant negative correlation was present between change in VEGF concentration and change in IDS-SR at Tx30 ($r = -0.371$, $p < 0.054$), reflecting that greater increases in VEGF were linked to greater improvement in depressive symptoms following the standard 6-week course of TMS. VEGF levels did not differ by sex or with age.

Conclusions: Patients with a successful treatment with TMS had significantly greater increase in VEGF from baseline to after treatment compared to non-responders/non-remitters and a larger increase in VEGF was associated with greater improvement in depressive symptoms after TMS. This is the first report examining VEGF levels in depressed patients receiving TMS. This pilot study provides promising preliminary data of VEGF being an important mediator in the mechanism behind TMS' antidepressant effects and as a potential biomarker of clinical outcomes. Given these positive results, a larger study with more participants and healthy controls is being pursued.

Keywords: Vascular Endothelial Growth Factor, Repetitive Transcranial Magnetic Stimulation, Treatment Resistant Depression, Peripheral Biomarker, Astroglia

Disclosure: Nothing to disclose.

T91. Sex-Specific Role for Dopamine Receptor D2 in Dorsal Raphe Serotonergic Neuron Modulation of Defensive Acoustic Startle and Dominance Behavior

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Background: Serotonergic neurons modulate diverse behavioral and physiological functions. Increasingly, serotonergic neurons are described as a heterogeneous group comprised of distinct subpopulations specialized to regulate distinct biological processes and functions. One such subpopulation that modulates social behavior in mice is distinguished by expression of the type-II dopamine receptor (Drd2) and the pan-serotonergic transcription factor Pet1. These neurons, referred to as Drd2-Pet1, are inhibited cell-autonomously by DRD2 agonism in slice and when constitutively silenced in male mice, affects levels of defensive and exploratory behaviors. While brain slice electrophysiology demonstrates that their excitability is inhibited cell-autonomously via DRD2 signaling, the requirement for DRD2 receptor activity in these serotonergic neurons for specific behavioral outcomes is unknown. To query the functional requirement for DRD2 in Drd2-Pet1 neurons, we generated mice with serotonergic neuron specific deletion of the Drd2 gene (Drd2-CKO) and administered a panel of behavioral assays. Further, we probe sex-specific differences in Drd2-Pet1 neuron candidate gene expression, electrophysiology, and projection patterns.

Methods: We validated conditional deletion of Drd2 in serotonergic neurons of male and female Drd2-CKO mice

(postnatal day 90). We then assayed behavior in the following assays: open field, rotarod, elevated plus maze, tail suspension, forced swim, contextual fear conditioning, water T-maze, paired pulse inhibition (PPI), three-chambered social interaction assay, ($n = 14$ control: 8 male, 6 female and 12 Drd2-CKO: 7 male, 5 female), acoustic startle response ($n = 30$ control: 14 male, 16 female and 28 Drd2-CKO:13 male, 15 female), resident intruder assay of aggression ($n = 24$ control and 26 Drd2-CKO males) and the tube test of social dominance ($n = 47$ control: 24 male, 23 female and 47 Drd2-CKO: 24 male, 23 female). Additionally, we recorded auditory brainstem responses to assess hearing status ($n = 18$ controls: 10 male, 8 female and 14 Drd2-CKO: 7 male, 7 female). To examine sex differences in Drd2-Pet1 neurons we additionally compared candidate gene expression (by mRNA in situ hybridization), electrophysiological profiles, and axonal projection patterns in male versus female mice.

Results: We found that Drd2-CKO males, but not females, demonstrate increased winning against sex-matched controls in a social dominance assay (For males, control: 34.17% +/− 9 wins, Drd2-CKO: 65.83% +/− 9 wins, $p = 0.0065$, Mann-Whitney, two-tailed, U=166. For females, control: 51.3% +/− 8, Drd2-CKO: 48.7% +/− 8 wins, $p = 0.8123$ Mann-Whitney, two-tailed, $U = 253$). Drd2-CKO females ($p = 0.0011$, Two-way ANOVA), but not males ($p = 0.7745$, Two-way ANOVA) exhibited blunting of the acoustic startle response – a protective, defensive reflex. Indistinguishable from controls were auditory brainstem responses, locomotion, cognition, and anxiety- and depression-like behaviors. Analyzing Drd2-Pet1 neurons, we found sex-specific differences in neurotransmission-related transcript levels, in action potential duration, and in proportional distribution of axonal collaterals to auditory brain regions.

Conclusions: Here we show the importance of type-2-dopamine receptor (DRD2) expression on a select subtype of serotonin-producing neuron for normal auditory processing and for sex-specific behavioral responses. These behavioral sex differences could potentially be influenced by the identified sex-specific molecular and cellular features distinguishing male versus female Drd2-Pet1 cells. Related behaviors in humans too show sex differences, suggesting this work has translational relevance.

Keywords: Serotonin, D2 Dopamine Receptor, Behavior, Acoustic Startle Response, Social Dominance

Disclosure: Nothing to disclose.

T92. Continuation Magnetic Seizure Therapy to Prevent Relapse in Treatment Resistant Depression

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Background: Although Electroconvulsive Therapy (ECT) is highly effective for treatment-resistant depression (TRD), it is associated with adverse cognitive effects. Magnetic Seizure Therapy (MST) is a novel convulsive brain stimulation treatment that may be as effective as ECT but with fewer adverse cognitive effects because it avoids stimulation of deeper brain structures such as the hippocampus. Although there is a growing evidence base for the efficacy of MST in TRD during the acute phase of treatment, there have been no studies of continuation MST for the prevention of relapse following the acute phase. Since those with TRD are known to have very high relapse rates, it is important to determine if continuation of MST to sustain response can be an effective strategy.

Methods: Patients diagnosed with treatment-resistant unipolar or bipolar depression meeting response criteria after acute MST were offered continuation MST in a single-arm prospective, open-label trial. Continuation MST consisted of 12 continuation MST sessions with decreasing frequency over the course of 6 months, with additional booster sessions if their depression symptoms started to worsen. The primary outcome of this study was relapse of depression, defined as a rating of ≥21 on the 24-item Hamilton Rating Scale for Depression (HRSD-24) and non-response to booster sessions or drop out from the study, or psychiatric hospitalization. Secondary outcomes included the Beck Scale for Suicidal Ideation (SSI) and a comprehensive neurocognitive battery of 24 different tests.

Results: Thirty participants with TRD completed at least one assessment during continuation MST and were included in the analysis. In total, 10 (33.3%) relapsed, with no significant differences in survival times between unipolar and bipolar depression. Mean ± SD survival time was 18.6 ± 1.6 weeks. Fifteen (50%) participants required additional booster treatments. All 17 of the participants who achieved complete resolution of baseline suicidality after their acute MST phase remained free of suicidality during the continuation MST phase. No neurocognitive test scores worsened during continuation MST, and there was a significant improvement in verbal fluency. Consistency of autobiographical memory recall that had significantly decreased during acute MST did not change further during continuation MST. Cox regression analyses did not show any significant moderating effects on survival time from age, sex, diagnosis, stimulus parameters, post-acute (i.e., pre-continuation MST) HRSD-24 scores, or treatment resistance.

Conclusions: Over the course of 6 months with continuation MST, approximately two-thirds of all participants with TRD who had improved with acute MST remained well. Continuation MST demonstrated tolerability with regards to significant adverse cognitive effects. We also found that resolution of suicidal ideation was sustained. Future studies of continuation MST are required through blinded randomized controlled trials, and in particular there is a need to compare directly with ECT.

Keywords: Electroconvulsive Therapy, Magnetic Seizure Therapy, Depression, Bipolar Disorder, Major Depression Disorder

Disclosure: Nothing to disclose.

T93. Effect of Esketamine Plus Standard of Care (SOC) vs SOC on Time to Remission of Depressive Symptoms in Patients With Major Depressive Disorder With Acute Suicidal Ideation or Behavior: Results From a Pooled Analysis of Aspire I and II

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Background: Conventional antidepressants have delayed onset of action (4 to 6 weeks) and offer limited benefits in patients with major depressive disorder (MDD) and acute suicidal ideation with intent, a vulnerable population who need rapid symptom control. ASPIRE I and ASPIRE II, a pair of pivotal phase 3, identically designed, randomized, double-blind (DB), placebo-controlled, multicenter studies, demonstrated significantly greater reduction in MDD symptoms in adults with acute suicidal ideation or behavior treated with esketamine (ESK) plus standard of care (+SOC) at 24 hours after the first dose, as compared with placebo

nasal spray (PBO) + SOC. This post-hoc analysis on the pooled ASPIRE I and ASPIRE II studies was intended to explore the clinical benefits of ESK + SOC in shortening the time to achieving symptom remission in this patient population.

Methods: Adult patients with moderate to severe MDD (Montgomery Åsberg Depression Rating Scale, MADRS, total score >28) and active suicidal ideation with intent in the past 24 hours were randomly assigned (1:1) to receive either intranasal 84 mg ESK or intranasal PBO, administered twice weekly for four weeks, in addition to comprehensive SOC (defined as initial hospitalization and initiation or optimization of oral antidepressant treatment per clinical judgment and practice guidelines). Both studies consisted of 3 phases: Screening (within 48 hours prior to Day 1 intranasal dose), DB treatment phase (Days 1–25), and follow-up (Days 26–90). Depressive symptoms and severity of suicidality were assessed by the MADRS total score (0-60) and the clinical global impression of severity of suicidality revised version (CGI-SS-r, 0-6), respectively. Both were assessed at 24 hours post dose and at least twice per week during the DB phase and at varied time intervals during the follow-up phase (i.e., twice weekly during Days 28 – 39, weekly during Days 46 – 53, biweekly during Days 67–90). Kaplan-Meier product-limit method was used to estimate the median time to remission of depressive symptoms from randomization. Symptom remission was defined as: 1) MADRS ≤12 at any given visit (first remission event), 2) MADRS ≤12 for two consecutive visits (confirmed remission event), and 3) both MADRS ≤12 and CGI-SS-r ≤1 (not suicidal or questionable suicidal) for two consecutive visits (confirmed remission of depressive symptoms with CGI-SS-r ≤1). Patients were censored at the date of last non-missing assessment if no event was identified over the entire study follow-up (Days 1–90). Cox proportional hazards regression model was also used to estimate comparative treatment effect on time to symptom remission, including baseline score as covariate and study center and SOC antidepressant treatment as stratification factors.

Results: Pooled data from both studies (patients: 451 [ESK: 226; placebo: 225]) were used for this analysis. Patients had a baseline mean MADRS total score of 40 and median CGI-SS-r of 4 (markedly suicidal). ESK+SOC was found to significantly shorten the time to first remission compared to PBO+SOC (median time: 15 vs. 23 days; adjusted hazard ratio [HR]: 1.47; 95% CI: 1.13, 1.92; $p = 0.005$), with 65.2% (ESK+SOC) vs. 55.5%(PBO+SOC) of achieving first remission by Day 25 and 86.3% vs. 83.5% by Day 90. Patients receiving ESK+SOC also experienced a significantly shorter time to confirmed remission compared to patients receiving PBO+SOC (median time: 23 vs. 50 days; adjusted HR: 1.50; 95% CI: 1.12, 2.00; $p = 0.007$), with 54.2% (ESK+SOC) vs. 39.8% (PBO+SOC) of patients achieving a confirmed remission by Day 25 and 75.0% vs. 55.0% by Day 90. When considering remission in depressive symptoms with CGI-SS-r ≤1 as a composite endpoint, median time to this outcome was in favor of ESK+SOC over PBO+SOC (25 vs 52 days; adjusted HR: 1.42; 95% CI: 1.06, 1.91; $p = 0.020$), with 51.8% (ESK+SOC) vs. 39.0% (PBO+SOC) achieving a confirmed remission with CGI-SS-r ≤1 by Day 25 and 71.1% vs. 53.5% by Day 90.

Conclusions: Patients with MDD with acute suicidal ideation or behavior need a pharmacological treatment with rapid onset of effect to quickly relieve depressive symptoms. The ASPIRE studies demonstrated that patients achieved remission significantly faster when treated with ESK+SOC vs PBO+SOC. These findings support the use of ESK+SOC in treating adults with MDD with acute suicidal ideation or behavior.

Keywords: Major Depressive Disorder (MDD), Esketamine Nasal Spray, Suicidal Ideation

Disclosure: Janssen Research & Development, LLC: Employee (Self)

T94. Effect of BI 1358894 Co-Administration on the Relative Bioavailability of Rosuvastatin and Dabigatran: Phase I Study in Healthy Male Volunteers

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Background: BI 1358894, a small-molecule inhibitor of transient receptor potential cation channel subfamily C (TRPC), is being developed for the treatment of major depressive disorder. Rosuvastatin is a statin medication used to lower cholesterol in patients with high cholesterol, and is a sensitive probe substrate of the drug transporters breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, and OATP1B3.[1,2] Dabigatran is an anticoagulant used to treat and prevent blood clots, and is a sensitive probe substrate of drug transporter P-glycoprotein (P-gp).[3,4] This drug–drug interaction (DDI) study investigated the effect of BI 1358894 on the relative bioavailability of oral rosuvastatin and oral dabigatran etexilate.

Methods: This was a Phase I (NCT04099732), two-part, non-randomized, open-label, two-period crossover study in healthy male participants. All treatments were administered following a high-fat/high-calorie meal. In Part 1, period 1, participants received a single dose of rosuvastatin 10 mg; in period 2, participants received single doses of rosuvastatin 10 mg and BI 1358894 200 mg. In Part 2, period 1, participants received a single dose of dabigatran etexilate 150 mg; in period 2, participants received single doses of dabigatran etexilate 150 mg and BI 1358894 200 mg. For both parts, treatments were separated by a washout period of at least 7 days. The primary endpoints were area under the concentration–time curve (AUC) from time 0 to infinity (AUC0-∞) and the maximum measured concentration (Cmax) of rosuvastatin and dabigatran. The secondary endpoint was AUC from time 0 to the last quantifiable data point (AUC0-tz) of rosuvastatin and dabigatran. Safety and tolerability were assessed based on adverse events (AEs), safety laboratory tests, 12-lead electrocardiogram, and vital signs. The potential influence of BI 1358894 on rosuvastatin and dabigatran relative bioavailability was evaluated using analysis of variance (ANOVA) on a logarithmic scale; geometric mean exposure ratios were calculated for the primary and secondary endpoints. Descriptive statistics were calculated for all endpoints. Coproporphyrin I (CPI) and coproporphyrin III (CPIII) were evaluated within the rosuvastatin arm as endogenous biomarkers for the inhibition of liver-specific transporters OATP1B1 and OATP1B3 in order to identify if a potential interaction is more BCRP- or OATP-driven.

Results: All participants completed the trial (Part 1, $n = 14$; Part 2, $n = 12$) and mean age (standard deviation) was 47.1 (7.9) years and 39.7 (8.9) years for Parts 1 and 2, respectively. In Part 1, co-administration with BI 1358894 increased rosuvastatin Cmax, AUC0-∞, and AUC0-tz by 74%, 83%, and 86%, respectively, vs rosuvastatin administered alone. CPI and CPIII exposures were similar overall after administration of rosuvastatin alone and in combination with BI 1358894. In Part 2, co-administration with BI 1358894 increased dabigatran Cmax, AUC0 ∞, and AUC0-tz by 19%, 19%, and 20%, respectively, vs dabigatran administered alone.

Treatment-emergent AEs (TEAE) were reported for 10/14 (71.4%) participants in Part 1. Nervous system disorders were the most frequent (9/14 [64.3%]); 1/14 (7.1%) after receiving rosuvastatin alone and 9/14 (64.3%) after co-administration of rosuvastatin and BI 1358894. TEAEs occurred in 5/12 (41.7%) participants in Part 2. Nervous system disorders were the most frequent (5/12 [41.7%]); 2/12 (16.7%) after receiving dabigatran

alone and 4/12 (33.3%) after co-administration of dabigatran and BI 1358894. Overall, two TEAEs of severe intensity were reported (Part 1: headache; Part 2: nasopharyngitis). All other TEAEs were mild to moderate in intensity.

Conclusions: Coadministration with BI 1358894 increased the relative bioavailability of both rosuvastatin and dabigatran. In the rosuvastatin trial ($n = 14$), there was no indication of an effect on CPI and CPIII, suggesting that that OATP1B is likely not involved in the DDI effect of BI 1358894 on rosuvastatin and thus indicating that the DDI effect is primarily mediated through BCRP. Rosuvastatin and dabigatran were well tolerated when administered alone and moderately tolerated when administered in combination with BI 1358894 by the healthy male participants in this study.

Funding: Boehringer Ingelheim International GmbH (NCT04099732)

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Keywords: Major Depressive Disorder, Rosuvastatin, Dabigatran, BI 1358894

Disclosure: Boehringer Ingelheim Pharma GmbH & Co. KG: Employee (Self)

T95. The Patient Perspective: Esketamine Treatment for Major Depressive Disorder With Active Suicidal Ideation and Intent

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Background: Esketamine nasal spray (ESK) in conjunction with standard-of-care (SOC) (including oral antidepressant therapy) is effective in reducing depressive symptoms as assessed by clinician-rated outcome measures. We evaluated the effect of ESK on patient-reported outcomes (PROs) in patients with major depressive disorder (MDD) having active suicidal ideation with intent (MDSI).

Methods: Patient-level data were pooled from two randomized, double-blind, placebo-controlled, multiregional studies (NCT03039192 and NCT03097133) of ESK

(84 mg)+SOC in patients (males and females, age 18–64 years) with MDSI. ESK or placebo nasal spray (PBO) were administered twice weekly for 25 days in the double-blind phase of the study. All PRO data were collected using an electronic tablet and included hopelessness (Beck Hopelessness Scale [BHS]); quality of life (Quality of Life in Depression Scale [QLDS] and European Quality of Life Group, 5-Dimension, 5-Level [EQ-5D-5L]); and treatment satisfaction (9-item Treatment Satisfaction Questionnaire for Medication [TSQM-9]). Baseline to day 25 changes in BHS and QLDS scores (baseline to day 25) were analyzed using analysis of covariance and a mixed-effects model for repeated measures. Descriptive statistics were provided for baseline and day 25 EQ-5D-5L and TSQM-9 scores. Since the PROs were not the primary endpoints, sample size for each study was calculated using the primary endpoint – Montgomery-Asberg Depression Rating Scale (MADRS) total score. On assuming an effect size of 0.45 for the change in MADRS total score between ESK and placebo, a two-sided significance level of 0.05, and a drop-out rate at 24 hours of 5%, approximately 112 subjects were required to be randomly assigned to each treatment group to achieve 90% power.

Results: Pooled data for ESK+SOC ($n = 226$) and PBO+SOC ($n = 225$) were analyzed. Mean patient age in the ESK+SOC and PBO+SOC groups was 40.5 and 39.6 years, and the proportion of females was 59.3% and 62.2%. Baseline mean (SD) scores for ESK+SOC and PBO+SOC groups were: BHS (15.4 [4.2] vs 15.8 [4.3]), QLDS (22.2 [3.8] vs 22.0 [3.7]), health status index (HSI) (0.56 [0.20] vs 0.56 [0.20]), and EQ-Visual Analogue Scale (EQ-VAS) (40.1 [23.6] vs 40.2 [23.8]). Mean (SD) changes from baseline in BHS total score for ESK+SOC and PBO+SOC groups were −7.4 (6.7) vs −6.8 (6.5) and difference of least squares mean (95% CI) was −1.0 (-2.2, 0.21). Similar changes in QLDS score for ESK+SOC and PBO+SOC groups were −6.6 (6.1) vs −5.6 (6.0) and difference of LS mean (95% CI) was −1.4 (−2.5, −0.34). Relative risk (95% CI) of reporting perceived problems in EQ-5D-5L (levels 2–5) in ESK+SOC compared with PBO+SOC group were: mobility (0.78 [0.50, 1.20]); self-care (0.83 [0.55, 1.27]); usual activities (0.87 [0.72, 1.05]); pain/discomfort (0.85 [0.69, 1.04]); and anxiety/depression (0.90 [0.80, 1.00]). Mean (SD) changes (baseline to day 25) in ESK +SOC and PBO+SOC groups were (0.23 [0.21] vs 0.19 [0.22]) for HSI and (24.0 [27.2] vs 19.3 [24.4]) for EQ-VAS scores. Mean (SD) TSQM-9 scores at day 25 in ESK+SOC and PBO+SOC groups were (67.2 [25.3] vs 56.2 [26.8]) in the domain of effectiveness, (69.9 [25.2] vs 56.3 [27.8]) in global satisfaction, and (74.0 [19.4] vs 75.4 [18.7]) in convenience.

Conclusions: The PRO data provide support for the patient perspective of benefit associated with ESK+SOC treatment for depressive symptoms in patients with MDSI.

Keywords: Patient Reported Outcomes, Esketamine Nasal Spray, Major Depressive Disorder (MDD), Suicidal Ideation

Disclosure: Janssen: Employee (Self)

T96. Sex Differences in Stress Response Circuitry are Present in Early Adulthood: An fMRI Study of Healthy Young Adults

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Background: Stress is implicated in many chronic diseases. The increase in stress-related disorders in women begins post-puberty and persists throughout the lifespan. The connection between Major Depressive Disorder (MDD) and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is well established in preclinical and clinical research, with less work identifying sex-dependent effects. To understand pathological changes in stress response circuitry, we must first understand sex differences in stress response in healthy young adults. To that end, we created an MR-compatible task that combines elements of the Maastricht Acute Stress Test (MAST) and the Montreal Imaging Stress Task (MIST). The MAST was designed to elicit robust physiological stress responses by combining unpredictable physiological and psychological stress, whereas the MIST produces psychosocial stress and activation of arousal regions.

Methods: 42 healthy subjects aged 18-25 years (21M:21F) underwent functional MR imaging while performing a sustained stress task consisting of four components: baseline in scanner where subjects solved simple arithmetic problems (Pre-MAST); post-MAST in which subjects submerged one hand in ice-cold water while counting backward from 2043 in steps of 17; and MIST in which subjects did math problems beyond their

capability and were given negative feedback on their performance (MIST Pre-F and Post-F). Subjects completed questionnaires before and after scanning that measured anxiety (State-Trait Anxiety Inventory) and mood (Positive and Negative Affect Schedule).

Whole brain and small volume correction (SVC) in regions of interest (ROIs) using two-sample *t*-tests compared brain activation and conditions between sexes. ROIs included medial prefrontal cortex (mPFC), OFC, anterior cingulate cortex (ACC), hypothalamus, amygdala, and hippocampus. In addition, a general linear model (GLM) was used to test for sex differences in brain activity associated with peak percent change in cortisol. Functional connectivity during stress conditions was examined using CONN and seed-to-voxel analyses using the same ROIs. Reported results were significant at a threshold of $p < 0.05$ (FWE- or FDR-corrected) at the cluster level and $p < 0.001$ (uncorrected) at the peak.

Results: Anxiety and mood before and after the task did not differ between men and women (STAI-State: $t(41) = -0.42$, $p = 0.68$; Positive Affect Schedule: $t(37) = -0.035$, $p = 0.97$; Negative Affect Schedule: $t(40) = -0.26$, $p = 0.8$). Peak percent change in cortisol from in scanner baseline also did not differ between sexes ($t(35) = 1.01$, $p = 0.32$).

GLM analyses showed that, relative to men, cortisol response in women was related to increased brain activation in prefrontal regions post-MAST and MIST post-F compared to pre-MAST. Regions showing relationships with cortisol in women included anterior PFC, OFC, and L vlPFC (k(E) = 2962, p-FWE = 1.8e-12, peak p-FWE = 0.002, t = 7.46) post-MAST and R vlPFC (k(E) = 2382, p-FWE = 6.6e-18, peak p-FWE = 0.0003, t = 8.22) during MIST post-F in whole brain analyses. In SVC analyses, women showed positive correlations between cortisol and activation in ACC (k(E) = 731, p-FWE = 9.4e-05, peak p-FWE = 0.004, t = 5.7), OFC (k(E) = 339, p-FWE = 0.007, peak p-FWE = 0.005, t = 5.5), and mPFC (k(E) = 311, p-FWE = 0.01, peak p-FWE = 0.003, t = 5.85) during MIST post-F compared to pre-MAST.

Univariate analyses comparing post-MAST to pre-MAST showed women had increased activation in ventromedial PFC (k(E) = 877, p-FWE = 0.0003, peak $p = 0.0002$, t = 4.5) in whole brain and in ACC (k(E) = 324, p-FWE = 0.002, peak $p = 0.0001$, t = 4.04) and mPFC (k(E) = 305, p-FWE = 0.003, peak $p = 0.00006$, t = 4.25) in SVC relative to men.

Functional connectivity comparing post-MAST to pre-MAST showed men with increased connectivity between mPFC and R dorsolateral prefrontal cortex (DLPFC) (p-FDR = 0.02, peak $p = 0.00003$, t = 4.51) and L amygdala and L DLPFC (p-FDR = 0.02, peak $p = 0.00002$, t = 4.67) relative to women. Relative to men, women were characterized by increased connectivity between R amygdala and precuneus (p-FDR = 0.01, peak $p = 0.000002$, t = 5.3) and mPFC and posterior cingulate cortex (p-FDR = 0.02, peak $p = .000007$, t = 4.97).

In analyses comparing MIST post-F to pre-MAST, men had increased activation in R precuneus (k(E)=1057, p-FWE = 0.002, peak $p = 0.0004$, t = 4.43) and increased functional connectivity between R hippocampus and L angular gyrus (p-FDR=.02, $p = 0.00001$, t = 4.79) and hypothalamus and R precuneus (p-FDR = 0.01, $p = 0.000004$, t = 5.17) relative to women.

Conclusions: Healthy men and women in early adulthood show distinct neural responses to different types of stress despite reporting similar subjective feelings of stress. In response to MAST, women displayed increased activation in inhibitory regions of stress response circuity whereas men were characterized by increased connectivity to cognitive control regions. Women also showed a strong relationship between peak cortisol response and activation in inhibitory prefrontal regions following MAST and MIST. For the MIST, men had increased activation and connectivity in regions of the default mode network including precuneus, angular gyrus, and mPFC. Results highlight sex differences that implicate different strategies for inhibitory control of arousal. Collectively, these findings contribute to our understanding of sex differences in response to negative stress, from which we can better understand how this deviates in a sex-dependent way in MDD.

Keywords: Cortisol Response to Stress, Sex Differences, Human Neuroimaging

Disclosure: Nothing to disclose.

T97. Not All Sleep Disturbance is Created Equal: Using Sleep Difficulties to Predict Symptoms of Mania in Bipolar I and II

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Background: Sleep loss has been shown in longitudinal studies to trigger mood episodes among individuals with bipolar disorder. Investigations into individual differences in these associations have revealed greater vulnerability among individuals with Bipolar I disorder relative to those with Bipolar II. Decreased need for sleep is a hallmark symptom of mania, however individuals with mania can experience co-occurring insomnia-like sleep disturbance. Sleep disturbance can vary across individuals to include difficulties with sleep onset, maintenance, or early morning awakenings, however little research has examined whether specific types of sleep disturbances may be more directly associated with manic symptoms. The current study aimed to explore whether difficulties with sleep onset, awakenings after sleep onset, or early morning awakenings were differentially related to manic symptoms in a large sample of individuals with bipolar disorder.

Methods: The present study analyzed baseline data collected from a longitudinal study of bipolar disorder. 843 individuals were diagnosed with Bipolar I and 236 individuals diagnosed with bipolar II. Manic symptoms were assessed using the clinician-administered Young Mania Rating Scale (YMRS), with the single sleep item removed, which asked whether there was a decrease in sleep duration or decreases in perceived need for sleep. Sleep disturbance was assessed using three items from the clinician-administered Hamilton Depression Rating Scale (HDRS) examining sleep onset, sleep maintenance, and early morning awakening difficulties. All models were adjusted for gender and age.

Results: Linear regression demonstrated that sleep difficulties significantly predicted symptoms of mania in bipolar I, $F(5,833) = 8.534$, $p < 0.001$, with sleep onset difficulties, $p < 0.01$, and early morning awakenings, $p < 0.01$ but not sleep maintenance difficulties, $p = 0.41$, demonstrating significant association with mania. For bipolar II, however, sleep difficulties did not significantly predict mood symptoms. Sex was not significantly associated with worse mood symptoms in the model.

Conclusions: The pattern of disturbed sleep may be important when considering associations with symptoms of mania in individuals with bipolar disorder. Sleep loss that is characterized by multiple awakenings may not confer the same risk for manic symptoms as when it results from later sleep onset or earlier offset. Findings are consistent with previous research demonstrating differential associations of sleep loss and manic symptoms across bipolar subtypes, as our findings indicated greater associations between sleep disturbance and manic symptoms in individuals with Bipolar I disorder, only. Future research should examine whether different subtypes of insomnia symptoms differentially predict manic episode trajectory.

Keywords: Bipolar Disorder, Sleep Disturbance, Insomnia

Disclosure: Nothing to disclose.

T98. The Acute Onset of Stress-Related Depression Is Encoded by CRF BNST Neurons

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Background: Chronic stress is a key risk factor for the development of Major Depressive Disorder (MDD), yet it is unknown how stress that is primarily psychological in nature is translated at the level of neurons to produce behavioral dysfunctions associated with MDD. The limbic forebrain region, Bed Nucleus of the Stria Terminalis (BNST), is an extension of the Amygdala that encodes the nature and chronicity of stress to organize behaviorally adaptive responses. Importantly, the Oval Nucleus of the BNST (BNSTov) contains an enriched population of Corticotrophin-Releasing Factor (CRF) neurons. These BNSTovCRF neurons are stress responsive and thereby may provide the neural link between CRF and depression. Employing a range of behavioral, molecular, and cell-type specific optogenetics and fiber photometry, we unveil a dimension to depression vulnerability that relies upon accumulated stress-exposure. In this study, we seek to elucidate CRF-related neural mechanisms that underlie depression onset that arise from unmitigated exposure to chronic stress.

Methods: To elicit stress-related depressive behaviors, the Chronic Social Defeat Stress (CSDS) paradigm was administered. CSDS consists of daily repeated 10-minute antagonistic encounters with CD-1 male mice, followed by a 24-hour sensory contact period over the course of 10 days. Male mice underwent behavioral assays that solicit for a range of anxiety and depression related behaviors including social interaction (SI), sucrose preference, and elevated plus maze tests. To manipulate the activity of BNSTovCRF neurons, Crf-Cre mice were injected with viral constructs (DREADDs, opsins, calcium-indicators) and ferrule cannulae implanted. To record electrical activity of BNSTovCRF neurons, Crf-cre::TdTomato reporter mice were used and cell-attached electrophysiology was used to record the spontaneous firing rate.

Results: We have discovered a discrete time-window between 7 and 10 days of CSDS, where mice rapidly diverged from baseline behavior to resilient or susceptible phenotypes (Two-way ANOVA, $p < 0.0001$, $n = 18$-20 mice per group), unmasking a temporal dimension to stress-susceptibility. Importantly, electrophysiological (susceptible vs resilient) and fiber photometric studies showed correlations of cell-type and circuit level neuroadaptive changes respectively with the behavioral observations. Cell-type specific chemogenetics reveal the necessity and sufficiency for BNSTov CRF neurons for promoting the development of depressive- and anxiety-like behaviors.

Conclusions: Altogether, these findings provide evidence of a temporal domain to stress adaptation where alterations in CRF neurotransmission may shift the predisposition of mice toward either stress-resiliency or stress-induced depressive-like susceptible phenotypes. This discrete period of neuroadaptation may present a window of opportunity for targeting molecular mechanisms with the possibility of preventing the onset of depression in stress-susceptible populations.

Keywords: Depression, Mood and Anxiety Disorders, Emotional Stress

Disclosure: Nothing to disclose.

T99. Pain Perception May Mediate the Relationship Between Sleep Abnormalities and Increased Risk for Suicide

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Background: Effective suicide prevention is hindered by a limited understanding of the neurobiology leading to suicide. Recognizing individuals at the highest risk for transition from suicidal thoughts to action and deciding when to intervene based on currently known risk and protective factors remains a subjective and fallible process. Both sleep and pain processing regulation abnormalities are found in individuals who attempt suicide. The close temporal association between sleep and pain dysregulation with suicidal behavior suggest that both phenomena may interact in the development of suicide risk. Our objective was to examine pain processing as a mediator of the elevated suicide risk associated with sleep abnormalities.

Methods: Three groups of adult depressed patients of both genders (ages 18-65 years) including recent suicide attempters ($n = 79$), suicidal ideators ($n = 131$) and non-suicidal depressed controls ($n = 51$) were examined in a cross-sectional study for sleep abnormalities, physical and psychological pain, pressure pain threshold, suicidal ideation and recent suicidal behavior. To evaluate the mediation effects of current physical/psychological pain, four series of regression analyses were performed in the Suicide Attempt and Suicidal Ideation groups: 1) sleep quality predicts current physical/psychological pain on; 2) current physical/psychological pain predict suicidal ideation severity; 3) sleep quality predicts suicidal ideation severity; 4) sleep quality + current physical/psychological pain predict suicidal ideation severity. Physical and psychological pain, pressure pain threshold and suicidal ideation severity were compared between patients suffering from nightmares vs. not, early insomnia vs. not, middle insomnia vs. not, terminal insomnia vs. not, any insomnia vs. not, and in patients waking up feeling rested vs. not using *t*-tests.

Results: Sleep quality was negatively correlated with suicidal ideation severity ($p = 004$); this correlation was mediated by both physical and psychological pain. The only difference in sleep-related measures between depressed patients with suicidal ideation and those after a recent suicide attempt was higher frequency of early insomnia in the former group ($p = 0.010$). Both current physical and psychological pain were increased in patients suffering from nightmares ($p = 0.003$; $p = 0.001$), early ($p = <0.001$; $p = <0.001$), middle ($p = <0.001$; $p = <0.001$), terminal ($p = <0.001$; $p = <0.001$) and any type of insomnia ($p = <0.001$; $p = <0.001$). Pressure pain threshold was elevated in patients suffering from any type of insomnia ($p = 0.013$).

Conclusions: Sleep abnormalities were found in both acutely suicidal groups, patients with current suicidal ideation and those after a recent suicide attempt. Moreover, our findings indicate that the association between poor sleep quality and increase in suicidal ideation severity was mediated by both physical and psychological pain. The impact of these findings lies in the identification of pain processing as a biological mechanism underlying the progression to suicidal behavior. We hypothesize that underlying decreased GABAergic transmission, may be responsible for the sleep and pain processing abnormalities seen in suicidal patients.

Keywords: Suicide, Suicidal Ideation, Psychological Pain, Sleep, Insomnia

Disclosure: Nothing to disclose.

T100. Efficient Methodology for Genotyping CYP2D6 and CYP2C19 for Neuropsychopharmacology

Abstract not included.

T101. Neuroimaging of Depression With Diffuse Optical Tomography During Repetitive Transcranial Magnetic Stimulation

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Background: Repetitive transcranial magnetic stimulation (rTMS) is an effective and safe treatment for depression; however, its potential has been stunted due to non-optimized targeting, unclear ideal stimulation parameters, and lack of information regarding how the brain is physiologically responding during and after stimulation. While neuroimaging is ideal for obtaining such critical information, previous modalities have been limited due to poor spatial resolution, along with significant noise interference from the magnetic spectrum. In this study, we used a novel diffuse optical tomography (DOT) device in order advance our understanding of the neurophysiological effects of rTMS in depression.

Methods: Healthy and depressed subjects aged 18–70 were recruited. Treatment parameters were standardized at the left dorsolateral prefrontal cortex with a magnetic field intensity of 100% of motor threshold, pulse frequency of 10 per second, a 4 second stimulation time and a 26 second rest time. DOT imaging was simultaneously acquired from the contralateral dorsolateral prefrontal cortex.

Results: Eight healthy and eleven depressed subjects were included for final analysis. Hemoglobin changes and volumetric three-dimensional activation patterns were successfully captured. Depressed subjects were observed to have a delayed and less robust response to rTMS with a decreased volume of activation compared to healthy subjects.

Conclusions: In this first-in-human study, we demonstrated the ability of DOT to safely and reliably capture and compare cortical response patterns to rTMS in depressed and healthy subjects. We introduced this emerging optical functional imaging modality as a novel approach to investigating targeting, new treatment parameters, and physiological effects of rTMS in depression.

Keywords: Human Neuroimaging, TMS, Depression

Disclosure: Nothing to disclose.

T102. Cortical Thinning and Peripheral Inflammation in Persons at High and Low Familial Risk for Depression

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Background: Depression is one of the most common and impairing mental illnesses, impacting around 7.1% of U.S. adults (National Survey on Drug Use and Health, 2018). The last decade has seen a substantial increase in the study of potential biomarkers for depression, with inflammatory biomarkers (e.g., IL-6; CRP) showing promise (Strawbridge, Young & Cleare, 2017). However, the study of depression biomarkers has yet to yield a mechanistic understanding of how the markers contribute to the disease, impact prospective determination of treatment response, or lead to the development of novel, targeted therapies (Schmidt, Shelton, & Duman, 2011). It has been suggested that the aforementioned limitations can be overcome by examining an array of biomarkers simultaneously. Examining brain-immune interactions would not only allow for a better understanding of the entire biological networks that are impacted in depression but may also yield more sensitivity and specificity in predicting the development of depression and treatment response (Papakostas, 2013). We thus sought to integrate two biomarkers for depression: brain thinning and peripheral inflammation. The present study leverages a three-generation sample of individuals at high and low risk for depression based on family history that has been followed for over 30 years (Weissman et al., 2016). We employ a nuanced approach to studying inflammatory markers, examining a comprehensive panel of 92 inflammation-related protein biomarkers.

Methods: Participants were recruited from a three-generation sample that included children and grandchildren (G2 and G3) at high- or low- familial risk for depression, as defined by the presence or absence of major depressive disorder (MDD) in the first generation (G1). The sample consisted of 50 participants (25 females; 25 males, ageM = 38 ± 13.9). Twenty-three subjects had a high familial risk for depression (i.e., proband met MDD diagnosis at start of study), and 27 had a low familial risk for depression. Participants underwent Magnetic Resonance Imaging (MRIs), completed assessments of depressive symptomatology, and provided saliva samples. FreeSurfer (v6.0) was used to estimate cortical thickness at each point on the pial surface. Five cortical regions were examined (right superior frontal, left superior frontal, left caudal middle frontal, right caudal middle frontal and left inferior parietal). Regions of interest were selected a priori based on previous work from our group documenting persistent cortical thinning in these regions in high-risk offspring, therefore suggesting cortical thinning as a stable biomarker for familial vulnerability for depressive illness (Hao et al, 2019). Ninety-two inflammatory markers were simultaneously examined using the Olink® inflammation protein panel.

Results: High risk participants showed increased inflammation across five markers (IL-17A, IL-15RA, CCL23, IFN-gamma, & TRAIL; ps < 0.042; controlling for BMI, sex, & age). TRAIL was related to cortical thinning in the right caudal and superior frontal areas and IFN-gamma to thinning in the left caudal middle frontal area (rs < −0.293, ps < 0.048). Inflammatory markers were also related to symptoms of depression and rumination, including the Inventory of Depression and Anxiety Symptoms (IDAS), lassitude, insomnia, appetite gain, social anxiety, traumatic intrusions and traumatic avoidance subscales, as well as symptoms of rumination (all rs > 0.409, ps < 0.019).

Conclusions: Results suggest that inflammation may be implicated in both the brain changes seen in familial risk for and current symptomatology. Longitudinal research is needed to better understand how peripheral inflammation and cortical thinning- related to a family history of depression interact in predicting subsequent risk for depression. Although findings need independent replication, this study joins a growing literature in suggesting immune pathways may be a valid target for treatment.

Keywords: Inflammatory Markers, Depression, Cortical Thickness

Disclosure: Nothing to disclose.

T103. Inflammation in Bipolar Disorder: Age as Moderator That May Heighten Vulnerability to Infection

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Background: Evidence suggests a dysregulation in peripheral inflammatory markers in bipolar disorder (BD). Chronic somatic comorbidities associated with immune dysregulation are more prevalent in BD than in the non-mentally ill comparison (NC) subjects, and aging itself can be characterized as a chronic inflammation or "inflammaging". Age, comorbidities, and dysregulation of the immune system all predispose to a more severe COVID-19 outcome. People with severe mental illness, like BD, may have worse COVID-19 outcome, and it is important to understand who is most vulnerable in order to minimize morbidity and mortality during a pandemic.

Methods: We analyzed longitudinal data from patients with BD ($n = 52$; M/F: 29/23) and age-/gender- matched NC ($n = 74$; 38/

36), aged 25–65 years. Blood was drawn 3 times one week apart prior to the COVID-19 pandemic. 18 inflammatory markers in peripheral blood were analyzed: CRP, BDNF, CCL11, CCL26, IP10, MCP1, MDC, MIP1b, VEGF, Fractalkine (Fract), IFNg, IL6, IL8, IL10, TNFa, SAA, ICAM1, VCAM1. Acute inflammation (CRP>10mg/l or WBC>11000/ul) was excluded and means across samples computed. Somatic comorbidity was assessed as total severity index (SI) from the Cumulative Illness Rating Scale-Geriatric. General linear models were used to investigate the relationship of inflammation to age and SI in BD and NC, and to compare group relationships, in an exploratory approach.

Results: Levels of MDC ($p < 0.05$), IL6 ($p = 0.01$), TNFa ($p = 0.03$) and somatic comorbidity ($p = 0.02$) were higher, and of Frac ($p = 0.04$) lower, in BD vs NC. Older participants had higher IL10 ($p = 0.03$), MCP1 ($p < 0.01$), VEGF ($p = 0.02$), IFNg ($p < 0.01$), IL8 ($p < 0.01$), TNFa ($p < 0.01$), ICAM1 ($p < 0.01$), and VCAM1 ($p = 0.03$). Higher SI was associated with higher levels of VEGF ($p < 0.01$), IL6 ($p < 0.01$) and BDNF ($p = 0.04$). Further, there was an SI*group interaction for IP10 and MCP1, with positive relationships in NC and inverse relationships in BD.

For ICAM1, an age*group interaction ($p < 0.05$), indicated a stronger positive age relationship in NC vs BD.

Conclusions: These results provide evidence for immune dysregulation in BD, and greater inflammation with older age in both groups. In general, the effects of age and diagnosis were independent, with only the vascular endothelial marker ICAM1 showing stronger "inflammaging" in NC. Greater somatic comorbidity severity was also associated more inflammation in both groups; for some markers, this was true only in the NC group. Our results suggest that patients with BD might be generally vulnerable, irrespective of age, to worse COVID-19 outcome due to immune dysregulation already at young ages, as reflected by increased inflammation and comorbidities in BD vs NC. Since older age is related to heightened inflammation in both BD and NC, BD may reach concerning levels of inflammation sooner given their already elevated levels. We conclude that young and older people with BD and older NC are likely to be more vulnerable to worse COVID-19 outcomes.

Keywords: Bipolar Disorder, Ageing, Inflammation

Disclosure: Nothing to disclose.

T104. Cognitive Side Effects Are Associated With the Volumetric Increases in the Hippocampus During ECT

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Background: Electroconvulsive therapy (ECT) is considered to be the most effective treatment for major depressive disorder. However, the mechanism of action is unknown, and memory side effects are reported in a significant proportion of patients.

In recent large scale studies (N~300 patients) with the GEMRIC (Global ECT-MRI Research Collaboration) consortium we showed that ECT causes widespread volume increases across the brain in a dose dependent manner. Out of the tested 42 pair of regions hippocampus had the largest volume increase. Despite these robust findings, we could not find any correlation between the volume changes and the clinical outcome. There are clinical and preclinical reasons however to think that the hippocampus volume changes are more likely to be associated with the cognitive changes than with the clinical. We could not test this hypothesis in our previous studies as no neurocognitive measures were collected in the GEMRIC dataset. In this current study we set out to investigate this relationship.

Methods: The study contains two independent cohorts of patients ($N = 30$) who underwent a longitudinal neuroimaging study during their clinical ECT trial.

The first cohort contained 16 subjects (age: 33.9 ± 11.2 y, 9 F) with major depressive disorder who, received bifrontal only ECT treatment. We tested the patients' clinical symptoms at every ECT session with 24 item Hamilton Depression Rating Scale (HAM-D) and the patients were having rigorous neurocognitive testing at baseline, before the 5th ECT and before the 12th ECT. Every patient in this study had two MRI imaging sessions, one at baseline and one after the 8th ECT.

The second cohort contained 14 subjects (age: 38.8 ± 12.7 y, 4 F) with schizophrenia spectrum disorder (SCZ) (schizophrenia, schizoaffective disorder, schizophreniform disorder) who received bitemporal ECT. We tested their clinical symptoms with Brief Psychiatric Rating Scale (BPRS) every week in the first month, and every two weeks during the last month. We also collected extensive neurocognitive testing with the MATRICS battery at baseline and at the end of the 8-week interval. Patients had MRI imaging at baseline and at 8th week visit.

At each imaging session we obtained T1-weighted images with high resolution (0.7 mm isotropic) MPRAGE sequence. Images were automatically processed with the longitudinal version of Freesurfer 6.0 (Reuter et al. 2012). We identified 42 bilateral regions (x subcortical volumes and y cortical thickness) and calculated the percent changes in these regions by calculating the 100x(region2-region1)/mean(region2+region1).

The primary outcome measure we tested was the cognitive change (T-Score differences between time points), the hippocampus volume change and their correlation.

Results: The clinical symptoms improved significantly in both cohorts. In the first cohort the HAM-D changed from 22.3 ± 5.2 to 10.8 ± 5.4 ($\chi2=16.4$, df = 1, $p = 0.00005$) and in the second cohort the BPRS change was 42.1 ± 10.0 to 34.2 ± 9.6 ($\chi2=3.8$, df = 1, 0.05).

In the first cohort the RBANS decreased with 2.7 points (CI: -5.8 - 0.4, t = 1.85, df = 15, $p = 0.08$) after 5 ECT and with 1.5 points (CI: -6.4- 3.4, t = 0.65, df = 12, $p = 0.53$) after 12 ECT. In the second cohort the MATRICS decreased with 3.2 points (CI: -13.9 -7.6, t = 0.65, df = 11, $p = 0.53$) after 8 weeks of treatment. None of these changes were significant, but results indicated significantly larger individual differences than it is expected based on neurocognitive data collected in healthy controls (ICC =0.79 vs 0.28). Seven patients in the first cohort and five patients in the second cohort experienced more than 7 points (1 quartile) of decrease in their overall standard scores after ECT.

In good agreement with our previous studies, both cohort showed significant increases in the hippocampus (cohort 1: t = 6.1, $p < 0.0001$, cohort 2: t = 4.82, $p < 0.001$) in addition to other medial temporal lobe regions.

The volume changes of the hippocampus and the cognitive score changes correlated significantly in both cohorts ($r = -0.52$ and -0.56 respectively, $p < 0.05$), indicating worse cognitive function with the enlargement of the hippocampus. Out of the tested areas (42 regions) only hippocampus correlated with the cognitive changes.

Although only exploratory result, but the hippocampus change correlated with clinical response in the schizophrenia patient cohort ($r = -0.61$, larger hippocampus was associated with better clinical outcome).

Conclusions: These results indicate that hippocampus volume increase is associated with the cognitive side effects of ECT across different patient populations (SCZ and MDD). This result is especially important in the light of growing longitudinal neuroimaging evidence that ECT causes both cortical and subcortical volume changes in a dose dependent way. The results

suggest that although volume increases are widespread in patients with growing numbers of ECTs, the cognitive side effects are specific to the hippocampus volume increase.

The two different patient population also hints that the mechanism of action to improve clinical symptoms might be different across different disorders. In the first MDD cohort, in good agreement with previous reports, neither volume changes in the hippocampus nor in other areas were correlating with clinical outcome. The second cohort, although preliminary, indicates that hippocampus increase is associated with clinical outcome in schizophrenia patients.

Keywords: Electroconvulsive Therapy, Major Depressive Disorder (MDD), Schizophrenia (SCZ)

Disclosure: Nothing to disclose.

T105. Phd Finger 21B Deficiency Leads to Increased Anxiety- and Depressive-Like Behaviors in Mice

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Background: We have recently found that the plant homeodomain finger protein 21B (Phf21b) gene, located in the genomic region in chromosome 22q13.31, is stress sensitive. Using a model of stress, we reported a significant decreased hippocampal Phf21b gene expression in rats resilient to chronic restraint stress compared to non-chronically stressed rats. The PHF21B gene, aka PHF4, is a member of PHD finger proteins with a conserved 531 amino acid protein that encodes a potential histone modification reader. Its gene expression is found to be expressed in several brain regions, including the frontal cortex and the hippocampus; though, its central nervous system (CNS) functions remain unknown. Therefore, we generated a Phf21b knockdown mouse model and characterized anxiety- and depressive-like behaviors.

Methods: The Phf21b mutant mouse was generated using the CRISPR/Cas9 technology at the SA Genome Editing Facility (University of Adelaide, South Australia, Australia). In this mouse model, most of exon 4 of the mouse Phf21b gene was deleted and a 5 bp random DNA insertion to create a frameshift mutation and a premature stop codon. We used behavioral assays to ascertain the effects of Phf21b deficiency in emotional behaviors in littermate wild-type (WT, Phf21b+/+), heterozygous (Phf21b+/Δ) and homozygous (Phf21bΔ/Δ) mice. Male and female mice were studied. Anxiety-like behaviors were measured in the elevated plus-maze (EPM) and open-field test (OFT). Depressive-like behaviors were measured in the tail suspension test and the sucrose preference test.

Results: Adult Phf21b WT and mutant mice were evaluated for general health. Litter-mates of the three genotypes had similar weight, length, and other physical characteristics, such as coat, skin and whisker appearances, and general activity. Male and female mice had similar changes in anxiety- and depressive-like behaviors, and their combined data were used for data analyses. Phf21b deficiency increased anxiety-like behaviors in the EPM and OFT (n< 17/group for each test). In the EPM, Phf21bΔ/Δ mice spent significantly less time in the open arms was vs. WT ($P < 0.001$). In the OFT, Phf21bΔ/Δ mice spent significantly less time in the center of the arena ($P < 0.001$). Mice with Phf21b deficiency had increased depressive-like behaviors. We performed the tail suspension test where the total immobile time is a behavioral despair measure. Immobility duration in Phf21bΔ/Δ mice was significantly increased vs. WT mice ($P < 0.001$). Phf21bΔ/Δ and Phf21b+/Δ mice had significantly decreased sucrose preference compared to WT mice ($P < 0.001$ and $P < 0.01$, respectively).

Conclusions: The current studies were motivated by our previous findings that the chronic stress response in rats modulated Phf21b gene expression. Male and female Phf21b deficient mice had increased anxiety- and depressive-like behaviors compared to WT mice. Further studies are needed to understand the pathophysiological mechanisms affected by Phf21b deficient.

Keywords: Animal Models, Depressive-Like Behavior, Anxiety, Behavioral Phenotyping

Disclosure: Nature Publishing Group: Honoraria (Spouse); Elsevier: Honoraria (Self)

T106. Auditory Mismatch Negativity as Event-Related Potential (ERP) Biomarkers for NMDA Receptor Antagonist Medications

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Background: The discovery of acute antidepressant effects of sub-anaesthetic doses of ketamine has prompted a paradigm shift concerning the neurochemical basis for treating major depressive disorder (MDD). Compared to the monoaminergic route, N-methyl-D-aspartate receptor (NMDAR) rapid antagonism demonstrates antidepressant effects based on facilitation of neuroplasticity. However, there is a need for detailed physiological biomarkers to accurately monitor the downstream mechanics associated with variations in receptor binding between drugs. Early animal model studies of focal infusion of NMDAR antagonists such as phencyclidine (PCP) has demonstrated reduction in Auditory Mismatch negativity (MMN) amplitude (Javitt et al., 1996). The MMN amplitude can be studied in human subjects non-invasively using EEG and has demonstrated sensitivity to NMDAR antagonism. However, studies suggest variations in the effects of different pharmacotherapies, motivating the need for clarity on the efficacy of MMN as a broad physiological marker of NMDAR activity.

Methods: We conducted a comparison of the effects of three different NMDAR antagonists on the MMN amplitude and latency in human subjects to investigate the phenotypical effects associated with different affinity and binding site properties.

Linear mixed models (LMM) were used to estimate effects of each NMDAR antagonist. The first study used two doses (1440 mg and 720 mg) of Kynurenine pathway modulator AV-101 (4-chlorokynurenine, 4-Cl-KYN), an oral prodrug of 7-chlorokynurenic acid (7-Cl-KYNA) relative to placebo, an NMDAR glycine site antagonist in ($N = 10$) healthy veterans in a randomized, double-blind, placebo-controlled cross-over trial. MMN was evaluated at baseline (pre-infusion), and then hourly intervals until 5 hours post dose. The second study conducted three 60-minute infusions of a selective "low trapping" NMDAR antagonist (Lanicemine, BHV-5500, 100mg) in PTSD patients with moderate symptoms. Patients were randomized into placebo/saline ($N = 12$) or Lanicemine infusions ($N = 11$). MMN was evaluated at baseline (pre-infusion), 30 minutes into infusion and 30 minutes after end of infusion at two sessions separated by 4 days. To evaluate the acute effects of Lanicemine, baseline measures on each day were used covariates in the LMM. The final study used a single subanesthetic dose of Ketamine (0.50 mg/kg) ($N = 10$) or midazolam ($N = 7$) infusion in older veterans (age 55+) with late-life treatment-resistant depression. MMN was measured at baseline, 30 minutes and 1

hour from start of the 40-minute infusion and 2 and 3 hours after end of infusion.

MMN task was a passive oddball task and consisted of standard tones (50-ms, 80-dB SPL, 1kHz standard tones) that occurred 90% of the time and deviant tones (100-ms, 80-dB SPL, 1kHz) that occurred 10% of the time. Each deviant was preceded by 5-14 standard trials. Interstimulus interval was 500ms. The auditory Mismatch Negativity (MMN) is evoked between 100 and 250 ms after an unexpected auditory event and is measured as the difference between (frequent) expected and (infrequent) unexpected stimuli in a passive oddball task (Lijffijt et al., 2019). EEG was acquired using a 64 channel (BrainProducts GmbH, EasyCap) at 1000 Hz sampling rate. Data was re-referenced to average, filtered at 59-61 Hz notch & 1-30 Hz bandpass of continuous data. Noisy data were removed prior to Independent Component Analysis (ICA) for artifact removal. MMN was computed on electrode FZ or CZ as the difference waveform of standard from deviant ERP waveforms. These two electrodes were identified across the studies to contain the maximum MMN amplitude. Maximal deviation within 100ms-250ms was determined as MMN peak amplitude. MMN peak latency was time that the peak occurred in ms.

Results: Analysis of the fixed effects for AV-101 demonstrated the there was no significant impact of dose on MMN amplitude ($F = 0.89$, $p = 0.41$) and latency ($F = 0.94$, $p = 0.39$) relative to placebo. Analysis of the fixed effects of Ketamine demonstrated no significant effects of drug group on MMN amplitude ($F = 0.03$, $p = 0.86$) but did identify a significant increase in latency in the ketamine group relative to the control ($F = 4.76$, $p = 0.03$). Finally, analysis of fixed effects of Lanicemine demonstrated no significant effects of drug group on MMN amplitude ($F = 3.919$, $p = 0.059$) and latency ($F = 0.903$, $p = 0.353$).

Conclusions: A recent meta-analysis revealed that MMN amplitude is suppressed and, with a lower effect size, latency increases after ketamine administration in chronic schizophrenia patients. (Rosburg et al., 2016). This effect is sustained for at least 30 min after end of infusion (Umbricht D 2000). However, there is also contradicting evidence of the low-affinity NMDAR antagonist memantine increasing MMN amplitude (Swerdlow NR 2016). In our comparison of effects from the three studies using different NMDAR antagonists, we failed to demonstrate reduction in MMN amplitude, but revealed some variability in the ability of NMDAR antagonists to delay the latency of MMN generation compared to inert or active placebo. The results from our studies highlight the need for future work to assess the relationship between the mechanism of action and properties of the task such as frequency vs. pitch deviancy. It is also possible MMN amplitude and latency lack general sensitivity in detecting NMDA receptor hypofunction in healthy individuals, PTSD patients and late-life TRD patients compared to patients with schizophrenia, where the most amount of empirical data is found.

Keywords: NMDA Receptor Antagonist, Auditory Mismatch Negativity, EEG/ERP Electrophysiology

Disclosure: Nothing to disclose.

T107. The Impact of Regulator of G-Protein Signaling 2 (RGS2) on Social Stress-Induced Behavioral Phenotypes

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Background: Chronic stressful experiences are a well-known risk factor for the development of psychiatric disorders such as major depressive disorder (MDD). Although many pharmaceutical therapies have been developed for treating mood disorders, over half of individuals that seek treatment do not respond positively, indicating a dire need for new treatments and thus new molecular targets for pharmaceutical compounds. Social defeat stress (SDS) is widely used in rodents for modeling stress-induced phenotypes such as social withdrawal and anhedonia, which are in part modulated by the nucleus accumbens (NAc). In rodents, stressful experiences induce molecular changes within the NAc that correspond with changes in these behaviors. A limitation of previous work is that most focus on males. This is problematic because sex differences exist in the prevalence of MDD, where women are twice as likely to develop MDD relative to men. Given this, it is imperative that studies on this topic consider sex as a biological variable.

Here we utilize the California mouse model of social defeat, where both males and females show similar levels of aggression, allowing for direct sex comparisons at the behavioral and molecular level. Using RNAseq we have found a potential novel molecular target, Regulator of G-protein signaling 2 (Rgs2), which functions as a negative regulator of G-protein coupled receptor (GPCR) signaling. Reduced production of RGS2 protein interferes with the function of neuropeptide and neurotransmitter receptors and has been correlated with increased risk for neuropsychiatric disorders. In the following studies we use molecular techniques to confirm the impact of stress on Rgs2 and the relevance of Rgs2 to affect behavior using viral vector manipulations.

Methods: Experiment 1: male and female California mice were randomly assigned to SDS (placed in the cage of a same-sex aggressor for 7 min for 3 days) or control handling. 2 weeks later the NAc was dissected from stressed and unstressed males and females (unstressed = 7-8, stressed = 6-7) and used to perform RNAseq on an Illumina NextSeq platform. Following preprocessing differential expression (DGE) was performed using DESeq2 (R) and differences in transcriptional profiles between experimental groups were assessed using various techniques.

Experiment 2: in separate cohorts of mice, male and female California mice were randomly assigned to SDS or control handling. 2 weeks later samples were used for either in-situ hybridization to test the anatomical distribution of Rgs2 or the NAc was microdissected and used for either western blots or qPCR to test the effects of stress on RGS2 protein and mRNA expression.

Experiment 3: female California mice were run through SDS. 1 week later they were site-specifically injected with either an HSV vector expressing Rgs2 (I/E 4/5-HSV-RGS2-mCMV-eGFP) or an empty vector containing GFP into the NAc. 4 days later mice were run through a sucrose anhedonia test (to assess changes in preference for rewarding stimuli), followed by a social interaction test (to assess changes in interest in approaching a same-sex novel mouse). Mice were then transcardially perfused and viral placement was confirmed.

Statistical analysis: Exp. 1: *t*-tests followed by false discovery rate (FDR) analyses were used to compare DGE between groups. Exp. 2-3: data was normalized when appropriate followed by ANOVA testing and pairwise comparison post-hoc analyses.

Results: Using an unbiased rank-rank hypergeometric overlap analysis, we compared California mouse transcriptional profiles to profiles observed in the NAc of patients with and without MDD (MDD = 13, control = 9-13). We found 1) a lack of an overlap in directionality of transcriptional patterns (upregulated v. downregulated) between stressed male and female California mice, indicating SDS induced sex-specific changes to the transcriptome, and 2) an overlap in genes downregulated by stress in female California mice and in women diagnosed with depression.

Gene ontology analyses within this subset of downregulated transcripts in the NAc of both women and female mice showed

GPCR signaling, and regulation of GPCR signaling, were highly enriched terms. Rgs2 was contained within these enriched terms. In-situ hybridization analyses confirmed localization of Rgs2 in the NAc of California mice. Western blots and qPCR showed that SDS induced a significant reduction of RGS2 at the protein level ($p < 0.01$) and a trend for a decrease in Rgs2 mRNA ($p = 0.06$) in a sex-specific manner two weeks after stress exposure.

Using an HSV viral vector we show that upregulating Rgs2 following SDS reverses both stress-induced social withdrawal ($p < 0.01$) and anhedonia ($p < 0.001$) compared to stressed females receiving an empty vector and stressed females where either vector was misplaced (Rgs2 = 7, GFP = 6, miss = 4). Future experiments are planned to confirm whether shRNA down-regulation of Rgs2 can induce social withdrawal and anhedonia in unstressed female mice.

Conclusions: These results show that SDS induces similar transcriptional changes in female California mice and in women with depression, suggesting that SDS may be an important paradigm for assessing impacts of stress at the transcriptional level that are especially relevant for women. Additionally, we show significant evidence for Rgs2's ability to modulate depression-like behavioral phenotypes, demonstrating its potential to be a novel molecular target for therapeutic interventions for mood disorders.

Keywords: Mood and Anxiety Disorders, Nucleus Accumbens, Social Withdrawal, Depression, RNAseq

Disclosure: Nothing to disclose.

T108. Subjective and Behavioral Effects of Repeated Microdoses of LSD in Healthy Human Volunteers

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Background: Over the past several years there has been renewed interest in using lysergic acid diethylamide (LSD) and other psychedelic drugs to treat a range of psychiatric and medical conditions. In particular, the media has focused on the practice of 'microdosing' LSD in order to improve mood and cognition. Thousands of people report that very low ("subthreshold") doses of LSD, taken once every 3-4 days, can produce a range of beneficial effects. However, until now, the effects of such repeated doses have not yet been tested in a placebo-controlled laboratory study in healthy volunteers.

Methods: In this preliminary study, we examined the effects of 13µg LSD administered four times, once every 3 days on subjective ratings and emotion processing tasks. Eight healthy volunteers participated in a within-subjects, placebo-controlled design with a two-week washout between the drug and placebo conditions. They completed mood questionnaires and behavioral tasks during the sessions and after completing all four sessions.

Results: Repeated administration of LSD at this dose produced subtle effects on emotion processing, compared to placebo. It reduced negative responses in a social rejection task after the four administrations. On the social rejection task LSD increased subjects' sense of control and ameliorated their drop in self-esteem after rejection. Further, the drug produced subtle effects on perception of emotional facial expressions. LSD did not affect cognitive performance.

Conclusions: The study showed that such a repeated dosing design is feasible and suitable for further research. Future studies with larger sample sizes and those including populations with clinical symptoms of anxiety and depression will be important next steps in the field.

Keywords: LSD Microdosing, Mood, Humans, Translational Research, Psychedelics

Disclosure: Nothing to disclose.

T109. Concurrent Improvement of Depressive and Anxiety Symptoms in Patients With Postpartum Depression Treated With the Oral Neuroactive Steroid Zuranolone

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Background: Postpartum depression (PPD) is one of the most common medical complications during and after pregnancy. In the United States, approximately 13.2% of mothers experience symptoms of PPD, varying by state from 9.7% to 23.5%. Women with PPD may have intense feelings of sadness, anxiety, and irritability, as well as a range of cognitive, social, and somatic symptoms. Anxiety is a prominent symptom of PPD, and is associated with more severe disease. Under- or untreated PPD is associated with negative short- and long-term consequences for the mother, infant, and family. PPD has also been associated with altered functional connectivity of the default mode network, salience, and central executive networks, and altered GABAergic signaling has been implicated in PPD. Enhancing GABAergic inhibition may restore excitatory/inhibitory balance to regulate brain network activity, which has been proposed to reduce depressive symptoms. Zuranolone (ZRN; SAGE-217) is an investigational oral neuroactive steroid GABAA receptor positive allosteric modulator. Neuroactive steroids that act as GABAA receptor positive allosteric modulators activate both synaptic and extrasynaptic GABAA receptors to produce phasic and tonic inhibitory currents to potentially enhance GABAergic inhibition. ZRN was evaluated in a double-blind, randomized, placebo-controlled Phase 3 trial in adults with PPD (NCT02978326). In this trial, ZRN met the primary endpoint, reducing depressive symptoms assessed by change from baseline (CFB) in the 17-item Hamilton Rating Scale for Depression total score (HAMD-17) at Day 15 versus placebo (CFB±SE: ZRN: -17.8±1.04, placebo: -13.6 ±1.07, $p = 0.0028$). The most common AEs (≥5%) in the ZRN group were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation. Post hoc analyses examined concurrent improvement of depressive and anxiety symptoms at Day 15 and Day 45 (trial follow-up).

Methods: In this Phase 3 study, women ($N = 151$) ages 18-45, ≤6 months postpartum, with PPD (a major depressive episode beginning in the third trimester or ≤4 weeks postpartum), and a qualifying HAMD-17 total score ≥26, were randomized 1:1 to receive ZRN 30 mg or placebo for 14 days, with 4 weeks follow-up. Secondary endpoints included the CFB in the HAMD-17 at all other measured timepoints aside from the primary endpoint on Day 15, CFB in the Hamilton Rating Scale for Anxiety (HAM-A), and CFB in the Montgomery–Åsberg Depression Rating Scale (MADRS). These post hoc analyses explored concurrent improvement of depressive and anxiety symptoms using a combination of scales: HAMD-17 and HAM-A, or MADRS and HAM-A, at Days 15 and 45. Depression remission was defined as either HAMD-17 total score ≤7, or a MADRS total score ≤10. Improvement in anxiety symptoms was defined as a HAM-A total score ≤7. Concurrent improvement was defined using two scale combinations: a HAMD-17 total score ≤7 and a HAM-A total score ≤7, or a MADRS total score ≤10 and a HAM-A total score ≤7. Concurrent improvement rates were assessed using Fisher's exact test, while estimates for odds ratios (ORs) and 95% confidence intervals (CIs) for ORs were derived using generalized estimating equations models for repeated measures, adjusting for baseline covariates. Secondary

endpoints and post hoc analyses were not adjusted for multiplicity. Adverse events (AEs) were assessed throughout the study.

Results: 76 and 74 patients from the ZRN and placebo treatment arms were included in these post hoc analyses, respectively. A significantly higher proportion of ZRN-treated patients achieved concurrent improvement of depressive and anxiety symptoms at Day 15 and Day 45 compared with placebo using both scale combinations. Namely, HAMD-17 and HAM-A concurrent improvement rates for ZRN-treated patients compared with placebo were 40.5% versus 19.2% ($p = 0.007$) at Day 15, and 52.1% versus 23.2% ($p < 0.001$) at Day 45. MADRS and HAM-A concurrent improvement rates for ZRN-treated patients compared with placebo were 43.2% versus 23.3% ($p = 0.014$) at Day 15, and 53.4% versus 26.1% ($p = 0.001$) at Day 45. ORs for HAMD-17 and HAM-A concurrent improvement were 2.8 (95% CI: 1.3, 5.8; $p = 0.008$) at Day 15, and 3.5 (95% CI: 1.7, 7.2; $p < 0.001$) at Day 45. ORs for MADRS and HAM-A were 2.4 (95% CI: 1.2, 4.8; $p = 0.019$) at Day 15, and 3.1 (95% CI: 1.5, 6.4; $p = 0.002$) at Day 45.

Conclusions: Zuranolone administration in women with PPD has previously been shown to provide rapid (Day 3 HAMD-17 total score) and sustained improvement in depressive symptoms (HAMD-17 total score at all measured time points up to Day 45) compared with placebo. In addition to these effects, post hoc analyses showed that a higher proportion of zuranolone-treated patients achieved concurrent improvement of depression and anxiety symptoms compared with placebo at both Day 15 and Day 45, as defined by HAMD-17/HAM-A or MADRS/HAM-A scores.

Keywords: Postpartum Depression, Anxiety, Zuranolone

Disclosure: Sage Therapeutics, Inc.: Consultant (Self)

T110. Lumateperone (ITI-007) in the Treatment of Bipolar Depression: Efficacy Across Symptoms

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Background: Approved treatments for bipolar depression are limited and are associated with a spectrum of undesirable side effects. Treatment options for depressive episodes associated with bipolar II disorder are even more limited. Lumateperone (lumateperone tosylate, ITI-007) is a mechanistically novel antipsychotic that is FDA-approved for the treatment of schizophrenia. Lumateperone simultaneously modulates serotonin, dopamine, and glutamate neurotransmission. In trials in patients with schizophrenia, lumateperone was efficacious with a favorable safety profile and improved depression symptoms in patients with moderate-to-severe depression symptoms at baseline. Lumateperone is currently being investigated for bipolar depression.

A phase 3 placebo-controlled study (NCT03249376) demonstrated the efficacy and safety of lumateperone monotherapy in patients with bipolar I or II disorder experiencing a major depressive episode (MDE).

Methods: Patients aged 18—75 years with a clinical diagnosis of bipolar I or II disorder experiencing a current MDE (MADRS Total score ≥20 and a Clinical Global Impression Scale-Bipolar Version-Severity [CGI-BP-S] score ≥4 at screening and baseline) were randomized to lumateperone 42 mg or placebo, administered once daily in the evening. MADRS Total and constituent item scores were analyzed by visit using a mixed-effects model for repeated measures approach. This prospectively defined analysis evaluated the broad efficacy of lumateperone across depression symptoms as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) single-item scores. Post hoc analyses included assessment of the percent of patients with categorical improvements in severity of individual MADRS items.

Results: In this 6-week study, 377 patients received treatment (lumateperone 42 mg, 188; placebo, 189) and 333 (87.4%) completed treatment. Lumateperone treatment significantly improved MADRS Total score compared with placebo (least-squares mean difference [LSMD] = −4.6; P<.0001).

The most prominent MADRS items at baseline were reported sadness (mean score: 4.2 [lumateperone], 4.1 [placebo]) and apparent sadness (3.9 both). With lumateperone treatment, 8 of 10 items significantly improved compared with placebo by Day 29, with significant improvement on all items by Day 43 (P<.05 to P<.001). The largest placebo-adjusted improvements (Day 43) were observed for reported sadness (LSMD = −0.6), apparent sadness (LSMD = −0.5), inner tension (LSMD = −0.5), and reduced sleep (LSMD = −0.7).

Conclusions: In patients with bipolar I or bipolar II depression, lumateperone 42 mg treatment compared with placebo significantly improved a broad range of depression symptoms.

Keywords: Bipolar Disorder, Antipsychotic, Bipolar I Depression, Bipolar I & II Disorder

Disclosure: Intra-Cellular Therapies, Inc: Employee, Stock/Equity (Self)

T111. The National Pregnancy Registry for Psychiatric Medications: Effects of Fetal Exposure to Atypical Antipsychotics on Risk for Major Malformations

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Background: The National Pregnancy Registry for Atypical Antipsychotics (NPRAA) is a systematic prospective pharmacovigilance program used to collect reproductive safety information in order to inform the care of reproductive aged women with psychiatric disorders. The Registry's scientific advisory board, consisting of experts in the fields of teratology, pharmacoepidemiology, and psychiatry, governs the release of findings.

Website: www.womensmentalhealth.org/pregnancyregistry

Toll-free number: 1-866-961-2388

Methods: Enrollment and longitudinal follow-up of participants is ongoing. Data are prospectively collected from pregnant women, ages 18-45 years, with three phone interviews conducted at time of enrollment, 7 months gestation, and 3 months postpartum. The exposed group in these analyses is composed of women who have taken one or more atypical antipsychotics during pregnancy, while the comparison group is composed of women with psychiatric disorders who have not taken this class of medication during pregnancy. Information regarding the presence of major malformations is abstracted from medical records, and identified cases of major malformations are adjudicated by a dysmorphologist who is blinded to drug exposure and psychiatric diagnoses.

Results: As of August 3rd, 2020, 2,004 women have enrolled, including $N = 923$ in the exposure group and 1,081 controls. Medical records were obtained for 81% of participants. Updated relative and absolute risks of major malformations for infants exposed to the 1) aggregate sample of atypical antipsychotics vs unexposed controls and 2) individual medications in the class vs the non-exposed comparison group will be presented (forthcoming August 2020). As of April 2019, $N = 1069$ women completed the study and were eligible for inclusion in the analysis. Of 535 live births in the group exposed to all atypical antipsychotics, 16 confirmed major malformations were reported.

There were 9 major malformations in the 534 live births of the control group. No consistent pattern of particular malformations was noted in either group. The absolute risk of neonatal major malformations was 3.0% in the exposure group and 1.7% in the comparison group. The estimated risk ratio for major malformations was OR= 1.77 (95% CI: 0.79-3.98).

Conclusions: The NPRAA offers a systematic way to collect prospective reproductive safety information which informs the care of women who may use atypical antipsychotics to sustain psychiatric well-being. This preliminary analysis indicates that SGAs do not appear to have a major teratogenic effect, but further information is needed to better estimate risk. The scientific advisory board for the NPRAA advised that risk estimates for malformations with respect to the newest sample of aggregate data be released with more specific risk assessments compared to risk estimates for individual molecules and the non-exposed control group. Forthcoming data will provide updated information regarding current findings from the NPRAA, pertaining to atypicals as a class and individual medications compared to controls. The importance of pregnancy registries is underscored by FDA guidance (https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule), and the inclusion of the National Pregnancy Registry for Psychiatric Medications in the FDA label for atypical antipsychotics among other medications.

Keywords: Pregnancy, Atypical Antipsychotics, Perinatal, Women's Health, Registry

Disclosure: Alkermes Biopharmaceuticals, Otsuka Pharmaceuticals, Sunovion Pharmaceuticals, Teva Pharmaceuticals, Janssen Pharmaceuticals, Sage Therapeutics, Inc., JayMac Pharmaceuticals, SAGE Therapeutics: Grant (Self); Alkermes Biopharmaceuticals, Praxis Precision Medicines, Inc.: Consultant (Self)

T112. Bioenergetic Effects of Ketamine and its Bioactive Metabolites in Human Cells

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Background: At subanesthetic doses, racemic ketamine and its bioactive metabolites induce rapid and robust antidepressant effects in treatment-resistant depressed patients and preclinical models of despair, e.g. chronic unpredictable stress and social defeat stress in rodents. On a cellular and molecular level, the antidepressant mechanisms of ketamine have mostly been investigated in non-human model systems. Although the upstream effects remain debated, most experts in the field agree that ketamine rapidly induces synaptogenesis/plasticity in a brain-derived neurotrophic factor (BDNF)-dependent manner. Synaptic remodeling is an energy-dependent process, and BDNF itself has been shown to enhance neuronal bioenergetics. To this end, we have investigated the in vitro effects of racemic ketamine and its bioactive metabolites, e.g. (2R,6R)-hydroxynorketamine (HNK), using a human neuroblastoma cell line, SK-N-SH cells. On differentiation, SK-N-SH cells have been shown to have cholinergic, dopaminergic and glutamatergic properties. In terms of the latter, differentiated SK-N-SH cells the express functional N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [Pizzi et al. (2002) Eur J Neurosci 16(12):2342-50, PMID: 12492429]

Methods: After plating at equal densities, SK-N-SH cells were differentiated for 2 weeks with a combination of retinoic acid and fetal bovine serum. These differentiated cells were treated with racemic ketamine and its bioactive metabolites in a dose- and time-dependent manner. Mitochondrial stress tests were performed in live cells using a Seahorse XFe24 analyzer (Agilent Technologies, Santa Clara, CA, U.S.A.]. These cells were sequentially incubated with inhibitors, e.g. oligomycin and rotenone & antimycin A, and uncouplers, e.g. carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone (FCCP), to assess mitochondrial and non-mitochondrial respiratory dynamics. Oxygen consumption rate (OCR) and extracellular acidification rate (ECR) were measured in ~30,000 cells/well with at least four (4) replicates per experimental condition. One-way analysis of variance (ANOVA) was used to compare group means in salient parameters.

Results: Ketamine and its bioactive metabolites had no consistent effect on ECR. Spare respiratory capacity percentage [(maximal respiration – basal respiration)/basal respiration] (SRC%) was increased in a dose- and time-dependent manner by racemic ketamine. Yet, with 1-hour incubations, up to 50 mcM ketamine increased SRC%, while, at higher doses (100 and 200 mcM), a reversal of these effects was observed. The highly selective N-methyl-D-aspartate (NMDA) receptor antagonist MK-801 (25 mcM) had similar effects on SRC% as racemic ketamine. 5 mcM rapamycin, an antagonist of the mTOR pathway, which has been demonstrated to have a mechanistic role in the antidepressant response of ketamine in preclinical studies, had no effect on investigated parameters including SRC%. Finally, (2R,6R)-HNK decreased non-mitochondrial oxygen consumption.

Conclusions: Racemic ketamine increase mitochondrial respiratory capacity in a dose- and time-dependent manner in differentiated neurons that express functional glutamate receptors. However, at higher doses, these effects are reversed, supporting the ketamine's "inverted U" hypothesis of antidepressant dose-dependency. NMDA-receptor antagonism alone appears sufficient to increase mitochondrial respiratory capacity, suggesting an important mechanistic role in this cell line. Finally, (2R,6R)-HNK, a bioactive metabolite with, in some studies, low affinity for NMDA receptors, decreased non-mitochondrial oxygen consumption, proposing a potential antioxidant-like effect. In the future, we will extend our respiratory studies to human induced pluripotent stem cell-derived cortical spheroids, a well-validated three-dimensional organoid model of cortical neogenesis and glutamate synaptic structure/plasticity.

Keywords: Ketamine, Hydroxynorketamine, Mitochondria, Respiration, Seahorse

Disclosure: Nothing to disclose.

T113. Anxiolytic-Like Activity of Cariprazine, a Dopamine D3 Receptor-Preferring Antipsychotic, in Rat Models

Abstract not included.

T114. (R,S)-Ketamine is Antidepressant and Prophylactic Against Stress in Adolescent but Not Aged Mice

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Background: (R,S)-ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is frequently used as an anesthetic in children. Recently, (R,S)-ketamine has emerged as a rapid-acting antidepressant, and we have reported that it can also be a prophylactic against stress in adult mice. However, it is still unknown whether (R,S)-ketamine can protect against stress in adolescent or aged populations.

Methods: Here, we administered saline or (R,S)-ketamine at varying doses (10, 30 or 100 mg/kg) to adolescent (5-week-old, $n = 10$ per group) and aged (24-month-old, $n = 6$ per group) 129S6/SvEv mice of both sexes, and assessed behavioral despair, avoidance, and perseverative behaviors 1 hour later. In a second set of experiments, to examine whether there was an interaction

of (R,S)-ketamine and stress, mice were administered saline or (R,S)-ketamine ($n = 4$-8 per group) 1 week or 1 month before a 3-shock contextual fear conditioning (CFC) stressor and behavioral despair, avoidance, and perseverative behaviors were assessed following stress.

Results: In adolescent mice, acute (R,S)-ketamine administration decreased behavioral despair ($p < 0.05$) and perseverative behaviors in females ($p < 0.0001$), and fear generalization in both sexes at sex-specific doses ($p < 0.0001$ in male and $p < 0.05$ in female mice). (R,S)-ketamine administered 1 week prior to CFC, attenuated learned fear ($p < 0.05$), avoidance ($p < 0.05$), and perseverative behaviors in female mice ($p < 0.0001$), and behavioral despair in male mice ($p < 0.01$). (R,S)-ketamine decreased fear generalization in both sexes ($p < 0.0001$ in male and $p < 0.05$ in female mice). (R,S)-ketamine administered 1 month prior to CFC attenuated learned fear in male mice ($p < 0.05$), and behavioral despair ($p < 0.05$) and perseverative behavior in female mice ($p < 0.01$). In all experiments, (R,S)-ketamine was not effective in aged mice ($p > 0.05$).

Conclusions: Our data indicate that (R,S)-ketamine is antidepressant and prophylactic at sex-specific doses (i.e., 30 mg/kg in male and 10 mg/kg in female mice) in adolescent, but not in aged mice. These findings underscore the need for sex- and age-specific dosing to increase the efficacy of (R,S)-ketamine treatment.

Keywords: Ketamine, Adolescence, Ageing

Disclosure: Nothing to disclose.

T115. Intranasal Administration of Transforming Growth Factor (TGF)-β1 Produces Rapid-Acting Antidepressant-Like Effects 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)-ketamine produced greater potency and longer-lasting antidepressant effects than (S)-ketamine in animal models of depression (Zhang J, et al. Pharmacol. Biochem. Behav. 2014; Yang C, et al., Transl. Psychiatry 2015). Using RNA-sequence and GSEA, we reported that transforming growth factor (TGF)-β1 plays a role in the antidepressant effects of (R)-ketamine (Zhang K, et al. Transl. Psychiatry 2020). The present study was, therefore, undertaken to examine whether intranasal administration of TGF-β1 can ameliorate depression-like phenotypes in the susceptible mice after chronic social defeat stress (CSDS) model.

Methods: Eight-week-old adult male C57BL/6 mice (weight, 20–25 g; Japan SLC, Inc., Hamamatsu, Japan) and male adult CD1 (ICR) mice, aged 13-15 weeks (body weight >40g, Japan SLC, Inc., Hamamatsu, Japan) were used. CSDS were performed as previously reported (Yang C, et al, Transl. Psychiatry 2015; Zhang K, et al. Transl. Psychiatry 2020). Saline (0.5 ml/kg), or TGF-β1 (1.5 and 3.0 μg/kg) was administered intranasally to CSDS susceptible mice. Furthermore, saline (0.5 ml/kg) was administered intranasally to control (no CSDS) mice. Behavioral tests such as locomotion, tail-suspension test (TST), forced-swimming test (FST), and 1% sucrose preference test (SPT), were performed. The data shown are the mean ± standard error of the mean (S.E.M.). Data were analyzed using one-way analysis of variance (ANOVA), followed post-hoc Tukey test.

Results: A single intranasal administration of TGF-β1 (1.5 and 3.0 μg/kg) significantly attenuated the increased immobility time of TST of CSDS susceptible mice. Furthermore, TGF-β1 (3.0 μg/kg) significantly attenuated the increased immobility time of FST of CSDS susceptible mice. Moreover, TGF-β1 (3.0 μg/kg) significantly ameliorated the decreased sucrose preference of SPT in the CSDS susceptible mice 2 days after a single injection.

Conclusions: The present study suggests that a single intranasal administration of TGF-β1 could produce rapid-acting and sustained antidepressant effects in CSDS susceptible mice. Therefore, intranasal administration of TGF-β1 would be a potential therapeutic drug for depression.

Keywords: Ketamine, R-(-)-Ketamine, Rapid-Acting Antidepressant, Chronic Social Defeat, Transforming Growth Factor Beta-1

Disclosure: Taisho: Consultant, Grant (Self); Dainippon-Sumitomo, Otsuka: Grant (Self)

T116. Insomnia, Wakefulness and Suicide Risk: The Relationship of Alpha and Beta Power With Next-Day Suicidal Ideation in a Treatment-Resistant Depressed Sample

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Background: Sleep difficulties, nocturnal wakefulness and insomnia have recently emerged as potential predictors of short-term suicide risk independent of psychiatric diagnosis. Previous work from our group using polysomnography (PSG) indicated that the amount of time spent awake in the 4 am hour predicts next-day suicidal thoughts in MDD and Bipolar Disorder patients. However, it is unclear if there are more specific neurobiological signals of wakefulness in the PSG/EEG waveforms known to be associated with arousal, specifically, frequencies in the alpha (relaxed wakefulness) and beta (alert wakefulness) frequency bands. Understanding this link between fluctuations in arousal-related frequencies and suicide risk could provide important neurobiological clues that could improve both risk prediction and treatment development. The aim of this analysis was to leverage the continuous and dynamic processes of alpha and beta EEG frequencies, and to test the hypothesis that patterns depicting temporally increasing and/or greater alpha and/or beta power would predict next-day suicidal thoughts in a sample of unmedicated patients with treatment-resistant depression (TRD).

Methods: 35 medication-free participants with TRD who participated in a double-blind placebo-controlled crossover trial completed overnight PSG. PSGs were performed following an adaptation night and before the first treatment/placebo. For each participant, 5.5 hours of raw data were used from sleep onset (1st non-wake epoch with average clock-time onset 11:37 pm) and recorded at C3-A2 (left central electrode). Estimated power spectral density (PSD) was applied with a multitaper approach for each of 4 alpha frequencies (8,9,10,11 hz), and each of 8 beta frequencies (18,19,20,21,22,23,24,25 hz). We then used a multilevel functional principal components (MFPCA) approach that accounts for multiple time series per person and preserves the continuous nature of the data by treating each frequency for each person as a continuous function of time. Eigendecompostion of smoothed covariance matrices generated eigenfunctions or curves that represent the primary patterns of variation evident in sleep processes. Principal component scores (PC scores) for alpha and beta frequencies were used to explore relationships with clinical measures. Next-day suicidal ideation (SI) with factor scores based on MADRS and BDI SI-related items were employed, as described in a published exploratory factor analysis. To estimate the relationship between SI and sleep processes associated with wakefulness, SI was regressed on the alpha and beta PC scores

separately while controlling for age and sex. Bayesian estimation and regression coefficient posterior distribution evidence ratios (probability a coefficient > 0 vs < 0; ratios > 1 indicating stronger evidence for a positive relationship) and posterior probabilities (probability in favor of hypothesis of positive, non-zero associations between SI and patterns of temporal fluctuations in alpha and beta frequencies) were used.

Results: For both alpha and beta MFPCAs, 4 principal component (PC) solutions that accounted for > 80% of the variance were used and omitted PCs that accounted for < 5% of total variation. The first component accounted for 63% of the total variance in the alpha MFPCA and 58% in the beta MFPCA. In each case, it represented a shift from the mean power over time. The second, third, and forth components respectively accounted for 9%, 7%, and 5% (alpha) and 9%, 7%, and 6% (beta) and represented oscillatory patterns with varying degrees of increasing and decreasing power over time. Evidence ratios (ERs) for alpha MFPCA PC scores as predictors of SI ranged from less than one (PC 3 ER = 0.10, posterior probability = 0.09; PC 1 ER = 0.22, posterior probability = 0.18) to greater than one (PC 2 ER = 1.13, posterior probability = 0.53; PC 4 ER = 4.53, posterior probability = 0.82). ERs for the first three beta MFPCA PC scores as predictors of SI were greater than 1(PC 1: ER = 4.41, posterior probability = 0.82; PC 2 ER = 4.53, posterior probability = 0.82; PC 3 ER = 7.0, posterior probability = 0.88). The ER for PC 4 was much weaker (ER = 0.59, posterior probability = 0.37). Notably, PC 3 from the beta MFPCA had the highest ER and was characterized by increasing beta power over the course of the night.

Conclusions: Leveraging the continuous, dynamic nature of wakefulness-related EEG frequencies, preliminary evidence indicated a possible association between increasing beta power over the 5.5 hours following sleep onset and next-day suicidal thoughts. Whether these effects are primarily due to SI or to factors such as depressive severity must be examined. Additionally, examination of night-to-night stability and statistical robustness of these findings is required to determine if increases in beta power over the night can identify real-time markers of suicide risk.

Keywords: Suicide, Sleep, Insomnia, Treatment Resistant Depression

Disclosure: Nothing to disclose.

T117. Postmortem Brain Desmosterol and 7-Dehydrocholesterol Concentrations in Depression

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Background: Major depressive disorder (MDD) is a common, disabling, and heterogeneous condition that responds unpredictably to current treatments. Identification of depression biomarkers is a promising and topical approach to personalized treatment and improved outcomes in MDD. We previously showed an association between depressive symptoms and plasma concentrations of two cholesterol precursors, desmosterol and 7-dehydrocholesterol (7DHC), which may be potential depression biomarkers.

Methods: Total cholesterol and sterol concentrations in postmortem brain samples from depressed ($n = 20$) and control ($n = 20$) subjects were measured with mass spectrometry. Both sexes were included. Bayesian statistical methods were used to calculate 95% credibility intervals and test the hypothesis that the differences in sterol concentrations associated with depressive symptoms in our previous study would be replicated in the comparison of depressed and control groups.

Results: Mean (± SEM) desmosterol concentration was 8.9 ± 0.97 ng/mg in the depressed versus 10.7 ± 0.72 ng/mg in the control group. The mean of the posterior probability distribution for the difference in desmosterol concentration between the two groups was 2.36 (95% highest density interval [HDI] 0.59–4.17). Mean 7DHC concentrations, 12.5 ± 4.1 ng/mg in the depressed versus 5.4 ± 0.74 ng/mg in the control group, were unlikely to be different (95% HDI, [-1.37–0.343]). However, 7DHC concentrations higher than the 95th percentile were associated with a diagnosis of MDD.

Conclusions: Desmosterol concentrations are lower in postmortem brains from depressed individuals compared to controls. Extremely high 7DHC concentrations in postmortem brains predict a lifetime diagnosis of MDD. These findings replicate the observations from a previous independent study examining plasma concentrations of these sterols in a population sample. Desmosterol and 7DHC may be promising leads for biomarker development in depression.

Keywords: Major Depressive Disorder (MDD), Desmosterol, 7-dehydrocholesterol, Biomarker

Disclosure: Nothing to disclose.

T118. Neurotensin Gates Valence-Specific Plasticity Underlying Associative Learning

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Background: The ability to differentiate between rewards and punishments (assigning positive or negative valence to environmental stimuli) is essential for survival. Aberrant valence assignment can manifest in many psychiatric disorders. Studies have shown that the reward and punishment association potentiates synaptic strength onto distinct populations of neurons in the basolateral amygdala (BLA), with projections to the nucleus accumbens (NAc) mediating reward learning and to the central nucleus of the amygdala (CeM) mediating fear learning. However, how the synaptic potentiation is directed to the appropriate projections remains unknown. Our previous finding has indicated a five-fold enrichment in the expression of the neurotensin receptor 1 (NTSR1) mRNA in the BLA-CeM neurons compared to the BLA-NAc neurons, suggesting a differential modulation of the neuropeptide, neurotensin (NT) on BLA projectors during valence-specific learning.

Methods: Adult wild-type C57BL mice, NT::Cre mice, and NT::Cre mice crossed with the Ai14 reporter line aged at least 2 months were used for experiments. For experiments involving gene manipulation and cranial implants, only male mice were used. Mice received stereotaxic injection of retrobeads in the NAc or CeM for labeling different BLA projectors, an injection of AAV encoding Cre-dependent ChR2 in the PVT for optogenetic stimulation of the PVT to BLA pathway, injections of AAV encoding SpCas9 in the PVT and a retrograde AAV encoding guide RNAs targeting exon 1 and exon 3 of the NT gene in the BLA for CRISPR-mediated NT gene inactivation, injections of AAV encoding Cre-dependent ChR2 in the BLA and a retrograde virus encoding Cre in the NAc or CeA for in vivo identification of BLA projectors. Mice were allowed 4-6 weeks of recovery before behavioral training. To assess associative learning, mice were trained with a Pavlovian conditioning paradigm, in which a 2 kHz or 20 kHz tone was

paired with either a 10ul 30% sucrose delivery or 0.6mA footshock for reward and fear learning paradigm, respectively. During the three-cued discrimination task, reward, shock, and neutral trials (which predicts no outcome) were chosen randomly at a 50%:25%:25% probability.

Results: We found that the bath application of NT differentially modulates synaptic inputs onto the BLA-NAc and BLA-CeM neurons and that the effects are blocked by NTSR1 antagonist. We further identified three NT afferents to the BLA, the paraventricular nucleus of the thalamus (PVT), medial geniculate nucleus (MGN), and ventral hippocampus (vHPC), all of which co-release glutamate. We showed that the input from the PVT is critically involved in valence processing. Specifically, optogenetic NT stimulation enhanced reward learning and suppressed fear learning, while CRISPR-mediated NT gene inactivation of the PVT-BLA pathway produced the opposite effects on reward and fear learning. Furthermore, in vivo electrophysiological recording revealed that the PVT-BLA NT inactivation diminished signal-to-noise ratio and disrupted valence encoding properties in all recorded BLA neurons, as well as in BLA projectors to the NAc and the CeA.

Conclusions: In summary, we have revealed a critical mechanism underlying neuropeptidergic modulation of valence assignment, which would potentially facilitate the development of novel therapies for related psychiatric disorders.

Keywords: Amygdala, Neuropeptides, Neurotensin, Valence, Associative Learning

Disclosure: Nothing to disclose.

T119. Neuronal Ensembles Underlying Monogamous Behavior in Nucleus Accumbens

Abstract not included.

T120. Microglial P2RY12 Mediates Chronic Stress-Induced Synapse Loss in the Prefrontal Cortex and Associated Behavioral Consequences

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Background: Chronic stress induces neuronal atrophy and synaptic loss in the medial prefrontal cortex (PFC), and this leads to behavioral and cognitive impairments. Recent studies in our lab demonstrate that microglia contribute to stress-induced synapse loss in the PFC, and microglia-mediated neuronal remodeling occurs in an activity-dependent manner. However, the pathways that drive microglial responses to altered neuronal activity in chronic stress remain unclear. Other work indicates that microglia respond to local release of purines, including ATP and ADP, following changes in neuronal activity through local release of purines (i.e., ATP, ADP). Indeed, purines released by neurons 'attract' microglia processes via the purinergic receptor P2RY12, which is exclusively expressed by microglia in the brain. In this way, P2RY12 signaling may drive functional changes in microglia, and subsequent structural remodeling of PFC neurons following chronic stress.

Methods: In the first set of studies male, wild-type or P2ry12 −/− mice were exposed to 14 days of chronic unpredictable stress (CUS) or handled intermittently as controls. In follow-up studies, wild-type male mice were exposed to CUS or handled intermittently as controls, and received daily injection of vehicle or clopidogrel (P2RY12 antagonist; 50 mg/kg). In both experimental approaches mice were assessed in the forced swim test (FST) and temporal object recognition (TOR) on subsequent days. Following behavioral testing, adrenal and spleen weight were measured to validate stress responsivity. In a separate cohort, frontal cortex microglia were assessed by fluorescence-activated cell sorting (FACS) and gene expression analyses. In another cohort of transgenic Thy1-GFP(M) mice, confocal microscopy was used to examine microglia morphology, dendritic spine density, and neuron-microglia interactions in the PFC.

Results: Consistent with prior results, CUS increased immobility in the FST and decreased discrimination in the TOR. These behavioral and cognitive consequences were attenuated in P2ry12 −/− mice and wild-type mice treated with clopidogrel. Flow cytometry and immunohistology confirmed that P2ry12−/− mice have deficient P2RY12 expression on microglia. Interestingly, clopidogrel treatment significantly reduced P2RY12 levels on microglia as well. Further analyses showed that clopidogrel altered other microglia markers (CX3CR1 and CSF1R) on frontal cortex microglia, regardless of CUS exposure. Confocal imaging in Thy1-GFP(M) mice showed that clopidogrel diminished the proportion of microglia with GFP+ inclusions, and prevented dendritic spine loss in the PFC following CUS, suggesting reduced microglial phagocytosis of dendritic elements.

Conclusions: Our data indicate that stress-induced alterations in neuron activity drive functional changes in microglia, and promote microglia-mediated neuronal remodeling through P2RY12 signaling. This work supports the idea that neuron-microglia interactions are critical mediators of synaptic function, and subsequent behavioral and cognitive consequences.

Keywords: Stress, Microglia, Prefrontal Cortex, Synapse, Neuroimmune

Disclosure: Nothing to disclose.

T121. Visuospatial Training Can Improve the Linguistic Abilities in Children With SLI

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Background: It is known that children with specific language impairments (SLI) have deficit in grammar understanding. It was proposed that this deficit in children with SLI is directly and exclusively related to language processes [van der Lely, 1998]. However, it was shown that children with specific language impairments have deficits not only in grammar understanding but also in non-linguistic cognitive abilities [Ullman & Pierpont, 2005]. Particularly, we have shown that children with SLI have weakness in visuospatial abilities. If our hypothesis is true, we can expect that visuospatial training can have positive effect not only on visuospatial abilities but also on linguistic abilities in children with SLI. The goal of this study was to assess the impact of visuospatial training on the language abilities in children with SLI.

Methods: The sample consisted of 26 children with SLI at 5-6 years of age (M = 5.36 years, SD = 0.96, 22 boys and 4 girls). Children were included and randomly assigned to training conditions according to a 2×2 cross-over design. We compared the efficacy of two methods of training (visuospatial training for children vs. conventional motor exercises) in a randomized controlled pilot study. Children from experimental group participated in 36 weeks of visuospatial training. This programme trains the child to do different visuospatial exercises both on motor and cognitive level. This training is built on the conceptual framework derived from the work of Luria's theory of restoration of neurocognitive functions [Luria, 1973].

We used the Luria's child neuropsychological assessment battery to assess language abilities in children before and after the intervention period. Children were assessed with the task "Comprehension of grammatical structures". The first part of this

task was designed to assess comprehension of reversible passive sentences. The second part assessed comprehension of sentences with prepositions that indicate the spatial relations between objects. To assess the visuospatial abilities in children we used 4 subtests from NEPSY (Arrows, Block Construction, Design Copying and Route Finding). Effects of visuospatial training were analyzed by means of an ANOVA for repeated measurements.

Results: The ANOVA has revealed ($p < 0.05$) that both for visuospatial abilities and grammar understanding subtests the visuospatial training was superior to the conventional motor exercises, with effect sizes in the medium-to-high range (0.65-0.89).

Conclusions: We have shown that visuospatial training can improve both visuospatial and linguistic abilities in children with SLI. The findings from this pilot study suggest that visuospatial training has positive effect on grammar understanding in children with SLI. Received results provided insight into cognitive and language mechanisms in typically developing children and the underlying nature of SLI, helping to elucidate the nature of impaired mechanism in children with weakness in grammar understanding. However, we need to do further investigations to prove our hypothesis about the underlying nature of specific language impairments.

Keywords: Language Delay, Visuospatial Ability, Neuroplasticity

Disclosure: Nothing to disclose.

T122. An Exploratory Proton Magnetic Resonance Spectroscopy Study of Chronic Pain in Veterans

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Background: Chronic pain (CP) affects more than 100 million Americans with an estimated cost of managing CP ranging between 560 and 635 billion dollars per year. Findings from CP studies indicate that CP is not a simple sensory experience but also involves cognitive/evaluative and affective components. In particular, CP has been associated with cognitive deficits in various domains of functioning including attention, working memory, and executive function. The cingulate cortex is a key region in pain perception and neuroimaging studies in humans have shown that CP alters normal processing in the anterior cingulate cortex (ACC), which could account for deficits in cognitive function. Proton Magnetic Resonance Spectroscopy (1H-MRS) is a non-invasive in vivo brain imaging technique that has been used to measure concentrations of several neurometabolites in the brain - specifically, N-Acetyl Aspartate (NAA), Creatine + phosphocreatine, Glutamate, gamma-Aminobutryic acid and Choline-containing compounds (phosphocholine and glycerophosphocholine (gpc)). However, investigations of CP using MRS have been limited thus far, and studies examining cognitive performance and its relationship to brain metabolites have not been reported. The goal of this study was to evaluate differences in MRS metabolites between Veterans with CP and those without CP. Based on previous findings, we hypothesized that the CP group would exhibit changes in metabolites that are involved in neuronal integrity (NAA), and brain phospholipid metabolism (gpc). A secondary aim focused on investigating the relationship between ACC neurochemistry and cognitive function in Veterans with and without CP to determine whether these associations differed by group.

Methods: In this cross-sectional study, Veterans with CP ($N = 61$, 72.7% male, average age=37.7) and no CP ($N = 19$, 94.4% male, average age=33.4) completed clinical interviews, self-report questionnaires detailing pain history, and cognitive tasks assessing verbal fluency, attention, and learning. Specifically, participants completed the California Verbal Learning Test, the Ruff 2&7 Selective Attention Test, the F-A-S Verbal Fluency Test, the Trail Making Test, and the Stroop test. Veterans also underwent single-voxel proton (1H) magnetic resonance spectroscopy (MRS) at 3 Tesla in the ACC using a two-dimensional (2D) J-resolved point spectroscopy sequence. Data were processed using the ProFit spectral fitting tool. All metabolite data are expressed as the ratio of individual metabolite concentrations to the ACC water signal. Group differences in demographic and clinical measures as well as metabolite ratios between CP and no CP groups were evaluated using Student's *t*-test or Mann-Whitney U test (if the variable failed the Shapiro-Wilk's test of normality). Spearman's correlation was run to test the relationship between metabolite ratios and cognitive performance.

Results: Veterans with CP exhibited lower levels of gpc/H2O ($p = 0.04$) and NAA/H2O ($p = 0.05$) in the ACC as compared to Veterans with no CP. Furthermore, although there were no significant between group differences in cognitive performance, the relationship between these metabolites and cognitive measures differed in the CP and no CP groups. In the no CP group, there was a negative relationship between gpc/H2O and Accuracy on the Ruff 2&7 Selective Attention Test (Spearman's rho $= -0.54$, $p = 0.02$); a positive relationship between gpc/H2O and Trail Making Test Part B Completion Time (Spearman's rho $= 0.50$, $p = 0.03$); and a positive relationship between gpc/H2O and Stroop Interference Completion Time (Spearman's rho $= 0.54$, $p = 0.02$). In contrast, these relationships did not hold true for Veterans with CP. With regard to NAA/H2O, Veterans with no CP exhibited a negative relationship with the total score on the F-A-S test verbal fluency (Spearman's rho $= -0.54$, $p = 0.02$) as well as with the total score from trials 1 to 5 in the CVLT (Spearman's rho $= -0.49$, $p = 0.03$). In contrast, these relationships did not hold true for Veterans with CP.

Conclusions: This study supports three main findings. First, the CP group exhibited lower levels of gpc in the ACC as compared to the no CP group. Gpc is a catabolite of phospholipids, which are the major structural components of cell membranes and thus plays a crucial role in energy utilization and bioenergetics in the brain. Decreased gpc may indicate decreased phospholipid synthesis, or an alteration in membrane phospholipid metabolism. Second, the CP group exhibited lower levels of NAA in the ACC as compared to the no CP group. NAA is considered a marker of neuronal integrity and mitochondrial function; hence, reduced levels of NAA in the ACC of the CP group may suggest reduced neuronal viability and mitochondrial dysfunction in the ACC for individuals with in CP. Prior studies in patients with chronic low back pain also showed reduction in NAA levels in the ACC. Finally, we identified a significant association between neurometabolites and cognitive performance in Veterans with no CP, which did not hold true in CP. Overall, these findings suggest a potential role of brain bioenergetics and mitochondrial function in CP, which may also mediate cognitive changes in this disorder.

Keywords: Chronic Pain, 1H MRS, N-acetylaspartate, Cognition, Choline

Disclosure: Nothing to disclose.

T123. Sex-Specific Disruptions in Social Behavior Following Early-Life Adversity: Role of IL-6?

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Background: Evidence suggests that increased production of central cytokines play a role in the pathophysiology of psychiatric

disorders such as major depressive disorder, schizophrenia, post-traumatic stress disorder, and bipolar disorder. Early-life stressors, like child abuse or sexual trauma, confers an increased risk for adult physical and mental illness and is associated with a chronic inflammatory state. Early-life experiences with caregivers can significantly alter the developmental trajectory. While most of our knowledge these relationships stem from mother-offspring interactions, increasing evidence suggests father-offspring interactions can prevent social, behavioral, and neurological impairments. However, to what extent adverse father-offspring interactions increase susceptibility to behavioral dysfunction and inflammation is unknown. The California mouse (Peromyscus californicus) is a genetically monogamous and biparental rodent species uniquely suited to investigate neural and behavioral consequences following a species-appropriate early-life adversity, namely paternal deprivation (i.e., permanent removal of the father on postnatal day 1).

Methods: To elucidate the relationships among early-life adversity, pro-inflammatory cytokine production, and social behavior, we examined IL-6 response in the brain following tests for sociability, social novelty preference, and social anxiety in adult male and female California mice reared under biparental or paternally-deprived conditions (n = 5–12/mice). To quantify sociability, mice were scored on measures of exploration in a central habituated area, a side chamber containing an unfamiliar same-sex conspecific (stranger 1) in an enclosure, or an empty side chamber. In a secondary test, preference for social novelty was quantified by presenting the test mouse with a choice between the first, now-familiar, same-sex conspecific (stranger 1) in one side chamber, and a second same-sex unfamiliar mouse (stranger 2) in the other side chamber. In a tertiary test, social anxiety was quantified by presenting the test mouse with a choice between the familiar, same-sex conspecific (stranger 1) in one side chamber and an empty side chamber. Outcome measures included time spent in each chamber. Following behavioral testing, mice were euthanized, brains were extracted followed by microdissection. Pro-inflammatory cytokine concentrations were determined using a Luminex™ 100 Multi-analyte System. For all analyses, males and females were analyzed separately via 2-way repeated ANOVA (chamber X rearing) or mixed-effects model (REML), where noted, followed by Tukey's multiple comparison test, when appropriate. Mean differences were considered statistically significant if $p > 0.05$. All experimental protocols were approved by the Institutional Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Results: Sociability. In males, a main effect of chamber ($p <$ 0.00) was observed, where more time was spent exploring the stranger and empty chambers, compared to the central habituated chamber. Rearing did not alter sociability behavior. However, in females, main effects of chamber ($p <$ 0.00) and rearing ($p =$ 0.04) were observed. While biparentally-reared females spent more time exploring the stranger and empty chambers, compared to the central habituated chamber, paternally-deprived females spent more time exploring the empty chamber, compared to the central habituated chamber. Social novelty preference. Among males, a main effect of chamber ($p = 0.0043$) was observed, where more time was spent, overall, exploring stranger 2. However, in females, a significant interaction between rearing and chamber (i.e., familiar vs. stranger 2) was observed ($p = 0.04$), such that biparentally-reared females spent significantly more time exploring the stranger mouse chamber compared to the center chamber; this effect was absent among paternally-deprived females. Social anxiety. A main effect of chamber was observed for both males ($p <$ 0.00) and females ($p <$ 0.00), with more time spent exploring outside of the central habituated chamber. IL-6. In males, IL-6 concentration did not differ as a result of an interaction between brain region and rearing, rearing alone, or brain region alone ($p > 0.05$, all comparisons; REML). However, in females, a significant interaction between rearing and brain region ($p = 0.02$) was observed. While IL-6 concentration was unchanged across brain regions in biparentally-reared females, IL6 was higher in the hypothalamus of paternally-deprived females, compared to the frontal cortex and hippocampus.

Conclusions: In sum, we observed 1) paternal deprivation reduces sociability in females, but not males, 2) paternally-deprived females, but not males, lack a preference for social novelty, 3) social anxiety is not driving the sex differences in social behavior, and 4) increased IL-6 production in the hypothalamus of the paternally-deprived female. Together, these findings suggest that paternal deprivation results in sex-specific disruptions to behavioral and neuroimmune responsiveness. To what extent increased IL-6 production underlies sex-specific deficits in social behavior following paternal deprivation should be further investigated.

Keywords: Early Life Adversity, Early Parental Loss, Sex Difference, Pro-inflammatory Cytokines, Social Behavior

Disclosure: Nothing to disclose.

T124. Novel PTPRD Phosphatase Inhibitors and Positive Allosteric Modulators for Addictions, RLS, Alzheimer's Disease Neurofibrillary Pathology

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Background: PTPRD. the receptor type protein tyrosine phosphatase D, is linked to neurofibrillary pathology densities in Alzheimer's disease (AD) brains, vulnerability to develop restless leg syndrome (RLS), vulnerability to develop a substance use disorder, abilities to quit smoking/stop abuse of opiates and brain levels of expression of PTPRD mRNA by human oligo- or polygenic association signals. Mouse models with reduced PTPRD expression provide support for AD, addiction and RLS phenotypes. Results suggest that drugs that inhibit PTPRD activity could be useful for addictions and that drugs that stimulate PTPRD activity could aid RLS symptoms and slow progression of neurofibrillary pathology.

Methods: Recombinant phosphatases from PTPRD and related phosphatases were purified from expressing E coli and the enzymes' abilities to dephosphorylate pNPP or phosphotyrosine substrates were tested in spectrophotometric assays and related to in silico modeling of the interactions. Compounds were synthesized based on our lead inhibitor and positive allosteric modulator structures, and tested using these assays and in in vivo assessments.

Mice with constitutive changes in expression of PTPRD were tested at young and older ages in standard mnemonic, locomotor, reward and motor assays.

Western analyses of brains of mice with constitutively- or pharmacologically-reduced PTPRD activity were tested for differences in tyrosine phosphorylation of putative phosphopeptide substrates.

Results: PTPRD's phosphatase in inhibited by our lead compound, 7-BIA, and by > 12 analogs with near or submicromolar potencies. 7-BIA displays significant potencies at PTPRS, PTPRS and PTPRJ. Analogs that model with interactions with each of two phosphatase binding pockets near the active site display modestly reduced relative potencies at PTPRS and PTPRF with more reductions in potencies at PTPRJ. PTPRD's phosphatase activity is stimulated by other lead compounds in ways that fit with reported dietary influences on progression to Alzheimer's disease and display greater relative efficacy and specificity at

PTPRD than at PTPRS or PTPRF. Mice with genetically or pharmacologically decreased PTPRD activity display increases in predicted phosphopeptides that serve as PTPRD substrates in vivo and hyperphosphorylators of tau, a principal component of neurofibrillary tangles. Aged mice with reduced PTPRD expression display behavioral differences consistent with PTPRD roles in neurodegenerations.

Conclusions: PTPRD's role as a target for AD, RLS and addiction pharmacotherapeutics is supported by these in vitro and in vivo observations. PTPRD phosphatase inhibitors and PTPRD phosphatase positive allosteric modulators can both be tolerated in vivo, and serve as lead molecules and therapeutics for these prevalent disorders.

Keywords: Alzheimers Disease, Addiction, Drug Discovery/ Development, Molecular Genetics, Cell Adhesion Molecules

Disclosure: Nothing to disclose.

T125. TRV045, a Novel, Selective S1P1 Receptor Modulator, is Efficacious in Reversing Neuropathic Pain Without Affecting Lymphocyte Trafficking

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Background: Painful peripheral neuropathies are common and often disabling conditions in clinical practice. Chemotherapy-induced peripheral neuropathy (CIPN) is a specific neuropathic pain condition that results from the use of a variety of chemotherapy agents and occurs in 30–40% of cancer patients. Similarly, a complication of diabetes mellitus is diabetic peripheral neuropathy (DPN), a condition affecting approximately one-third to one-half of patients with diabetes. Neither prophylactic nor symptomatic treatments have proven useful for treating CIPN, and currently available treatments for the burning, numbness and tingling associate with DPN are ineffective in a substantial proportion of patients.

Recent publications have suggested a beneficial role for non-selective sphingosine 1-phosphate receptor subtype 1 (S1P1R) modulators in treating neuropathic pain. However, current S1PR modulators are not selective for S1P1R and affect lymphocyte trafficking, limiting their utility for the treatment of neuropathic pain. Here we report the analgesic properties of a new chemical entity, TRV045, in rodent models of neuropathic pain. We also report evidence that TRV045 potently and selectively activates S1P1R, while having no effect on lymphocyte trafficking in rodents and non-human primates.

Methods: Hyperalgesia was induced in male C57BL/6 mice by injecting paclitaxel (6 mg/kg, i.p.) on Days 1, 3, 5, and 7. A baseline hyperalgesia score was recorded prior to paclitaxel dosing using the von Frey frequency testing method using a 0.4 g filament as the testing stimulus. TRV045 was administered subcutaneously at 0.1, 0.3 and 1 mg/kg (n = 6-7/group) on Day 14 or Day 19, with mechanical hypersensitivity measured prior to dosing and 30 min post-dose.

TRV045 was also tested for analgesic activity in the streptozotocin (STZ)-induced neuropathic pain model in male SD rats. S TZ (50 mg/kg) was injected intraperitoneally on Day 1 and hyperglycermia was confirmed on Day 3 by the presence of blood glucose >350 mg/dL. Reduced mechanical and thermal pain thresholds were confirmed on Day 13, reflecting the development of neuropathic pain. TRV045 was administered orally at 10, 30 and 60 mg/kg on Day 14 (n = 8/group) and mechanical allodynia and thermal hyperalgesia were tested at 30 and 60 min post-dose, respectively. Mechanical allodynia was measured using the manual von Frey test and thermal hyperalgesia was assessed by measuring hind limb withdrawal latency in response to a thermal stimulus.

Lymphocytes counts were determined in male C57BL/6 mice (n = 6–12/group) following 3 consecutive days of dosing with vehicle, 3.7 mg/kg TRV045 s.c. (approximately 25-fold higher dose compared to the calculated ED50 dose in the mouse CIPN assay) or 0.03 mg/kg fingolimod p.o. Lymphocyte counts were also determined in male cynomolgus monkeys (n = 3) following oral dosing with vehicle or 60 mg/kg TRV045.

Results: TRV045 dose-dependently reversed mechanical hypersensitivity induced by paclitaxel as measured by percent non-response to a 0.4 g filament. Following paclitaxel exposure, vehicle treatment led to a 27 ± 12% (mean ± SEM) non-response to the 0.4 g filament. TRV045 dosed at 0.1, 0.3 and 1 mg/kg s.c. produced a 51 ± 12%, 54 ± 13% and 90 ± 4% non-response, respectively, with a calculated ED50 dose of 0.15 mg/kg. The 1 mg/kg dose significantly reduced hypersensitivity (p < 0.01; one-way ANOVA followed by Tukey's multiple comparison test) compared to vehicle treatment, with efficacy comparable to a maximal efficacious dose of fingolimod (0.03 mg/kg p.o.; 73 ± 7% non-response).

TRV045 reduced STZ-induced mechanical allodynia and thermal hyperalgesia at rates similar to the positive control, 100 mg/kg p.o. gabapentin. Following STZ exposure, the paw withdrawal threshold was 1.7 ± 0.3 g in vehicle-treated animals and 13.8 ± 1.0 g in gabapentin-dosed animals (p < 0.001 vs vehicle; one-way ANOVA followed by Dunnett's test). Paw withdrawal threshold in animals dosed p.o. with TRV045 at 10, 30 and 60 mg/kg was 4.8 ± 1.2 g (p < 0.05), 9.7 ± 1.9 g (p < 0.001) and 10.9 ± 2.0 g (p < 0.001), respectively. Paw withdrawal latency was 7.1 ± 0.5 sec in vehicle-treated animals and 16.7 ± 1.3 sec in gabapentin-dosed animals (p < 0.001 vs vehicle). Paw withdrawal latency in animals dosed p.o. with TRV045 at 10, 30 and 60 mg/kg was 13.5 ± 0.9 sec (p < 0.001), 11.1 ± 1.0 sec (p < 0.001) and 13.9 ± 1.4 sec (p < 0.001), respectively.

Three days of TRV045 dosing at 3.7 mg/kg s.c. had no effect on absolute lymphocyte counts in mice. Six hours after the 3rd dose, lymphocyte counts were 4.9 ± 1.1E3 per µL, 5.6 ± 0.7E3 per µL and 1.1 ± 0.2E3 per µL in vehicle-, TRV045- and fingolimod-treated animals, respectively. Similarly, a 60 mg/kg p.o. dose of TRV045 had no effect on absolute lymphocyte counts in monkeys. Lymphocyte counts were 4.7 ± 0.4E9 per mL and 4.8 ± 0.7E9 per mL in vehicle- and TRV045-treated animals at 1 hr post-dose, respectively, and 5.2 ± 0.5E9 per mL and 5.4 ± 0.5E9 per mL in vehicle- and TRV045-treated animals at 24 hr post-dose, respectively.

Conclusions: TRV045 is a selective S1P1 receptor modulator that is an effective analgesic in rodent models of neuropathic pain. TRV045 differentiates from other non-selective S1P receptor modulators in that it does not cause lymphopenia. Therefore, TRV045 may provide a new therapeutic option for the treatment of neuropathic pain.

Keywords: Neuropathic Pain, Sphingosine 1-Phosphate Receptor, Chemotherapy-Induced Peripheral Neuropathy, Diabetic Peripheral Neuropathy

Disclosure: Trevena, Inc.: Employee (Self)

T126. Visual Area-Specific Inhibitory Control of Circuit Dynamics Modulated by an Elusive Inhibitory Basket Cell Subtype

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Background: In the neocortex, sensory perception is achieved by a two-way communication between primary and associative cortices and is controlled by a rich diversity of GABAergic interneurons. Inhibitory interneurons can be classified based on their morphological, molecular and functional properties as well as the specific synaptic pattern of connections they form with excitatory principal neurons.

In particular, perisomatic-targeting basket cells (BCs) form inhibitory synapses near the soma of the principal neurons (PNs) and efficiently modulate the firing of their postsynaptic targets. Perisomatic inhibition is provided by parvalbumin (PV)- and cannabinoid receptor type 1 (CB1)-expressing interneurons. PV BCs modulate the gain of contrast sensitivity and orientation tuning of visual responses in primary visual cortex (V1) and they drive network oscillations associated with cognitive function.

Despite the large body of evidence indicating the crucial role of PV cells in orchestrating cortical networks during sensory processing, the role of CB1 BCs is still unknown. However, this elusive – yet prominent – GABAergic cell type underlies several forms of cortical plasticity. Moreover, CB1 BCs are involved in the control of many physiological processes and in the emergence of several brain diseases, such as schizophrenia and autism. Previous studies showed that activation of CB1 receptors ameliorates visual perception in humans and rodents. However, the underlying mechanism remains unknown. Here, we aimed to elucidate the functional and synaptic properties of CB1 interneurons in visual areas V1 and V2M.

Methods: In order to identify the circuit properties of CB1 interneurons, we combined mouse genetics, in vivo two-photon calcium imaging in awake head-fixed mice, in vitro whole-cell patch clamp recordings and pharmacology. We used a mouse line in which td-Tomato is expressed by CB1-positive neurons (CB1-tdTomato mice). Mice were habituated for in vivo two-photon calcium imaging and we recorded the spontaneous activity of both PNs and CB1 positive interneurons while the mice rest or run on a treadmill. Neuronal activity was detected with the genetically encoded calcium indicator GCaMP6f, with viral labeling in V1 and V2M within layers 2/3 and recordings were achieved through a chronic cranial window. Analysis of the morpho-functional connectivity of CB1 BCs with layer 2/3 and 4 PNs was performed using in vitro whole-cell paired recordings.

Results: We found that CB1 expression was much stronger in V2M across L2-5 as compared to V1 and that L2/3 CB1 BCs from V2M projected to deeper cortical layers. Thus, in V1, CB1 BCs contact pyramidal neurons exclusively in layer 2/3, whereas in V2M they project both locally and to deeper layers. Moreover, layer 2/3 CB1-PN synapses of V2M were much weaker and more unreliable compared to their counterparts in V1. This was due to V2M-specific tonic CB1 signaling, which could be overridden by increasing the firing of presynaptic CB1 BCs. Consistently, in vivo, we found that spontaneous activity of PNs was lower in V1 than in V2M. Moreover, in V1, PN activity increased with locomotion, but, surprisingly, PNs were not modulated by locomotion in V2M. Systemic pharmacological blockade of CB1 receptors abolished the effects of locomotion on spontaneous activity of PNs in V1, and unmasked a modulation by locomotion of V2M PNs. Therefore, tonic CB1 signaling can confer a dynamic modulation of GABA release, which is visual area-specific. This will likely have significant effects in visual perception.

Conclusions: The malfunction of neuronal networks leads to devastating neurological and psychiatric diseases, including some forms of epilepsy, schizophrenia and autism. In particular, altered sensory perception is a prominent positive symptom of schizophrenic subjects. It is therefore of fundamental importance to understand the basic properties of specific neuronal networks, and how they underlie cognitive relevant responses.

Keywords: Visual Cortex, Cannabinoids, Inhibitory Interneurons, Two-Photon Calcium Imaging

Disclosure: Nothing to disclose.

T127. The Role of BDNF in Modulating Perseverative, Compulsive Behaviors

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Background: Perseverative, repetitive behaviors are found in common neuropsychiatric and neurodevelopmental disorders, such as obsessive-compulsive disorder (OCD) and autism spectrum disorder (ASD). Although circuit-level studies in both human neuroimaging and rodent optogenetic studies have shown that these repetitive behaviors result from an imbalance in the cortico-striatal-thalamo-cortical (CSTC) feedback loop, less is known about the underlying molecular mechanisms of how this imbalance occurs. Recent genome-wide association studies have shown that genetic variants of synaptic proteins involved in brain-derived neurotrophic factor (BDNF) signaling are more commonly seen in patients with OCD. In parallel, studies have shown that mice missing key postsynaptic scaffolding proteins, such as Sapap3 and Shank3, demonstrate increased repetitive grooming behaviors, increased anxiety-like phenotypes, and reduced sociability. These aberrant mice also show increased signaling of metabotropic glutamate receptor 5 (mGluR5), and inhibition of mGluR5 activity led to mitigation of these repetitive behaviors. Finally, mice lacking Slitrk5, a postsynaptic receptor that sorts BDNF receptor TrkB to the recycling pathway after BDNF binding, also exhibit increased repetitive behaviors with reduced BDNF-dependent TrkB signaling, specifically in the striatum. These studies suggest a link between BDNF-TrkB and mGluR5 signaling pathways to mediate synaptic plasticity. Our central hypothesis is that BDNF-TrkB-mediated mGluR5 signaling within the CSTC circuit, specifically in the connection from the medial orbitofrontal cortex (mPFC) to the nucleus accumbens (NAc), is involved in these pathologically perseverative, repetitive behaviors.

Methods: We used two BDNF loss-of-function mouse lines: a conditional BDNF knock-out mouse (BDNFfl/fl) and a haploinsufficient BDNF mouse (BDNF+/−). Male mice aged 2-4 months were used in this preliminary study. First, we injected an AAV-Cre virus into the mOFC of the BDNFfl/fl mouse for a targeted BDNF deletion within the mOFC-NAc circuit and observed their grooming behaviors ($n = 12$ GFP control, $n = 15$ AAV-Cre). Second, we examined the mGluR5 expression in the OFC and NAc of BDNF+/− mice using qPCR and western blot. We injected a selective mGluR5 positive allosteric modulator intraperitoneally to induce grooming behaviors and used fiber photometry to record the neural activity in the NAc during grooming bouts in BDNF+/− and wildtype mice ($n = 12$ WT, $n = 10$ BDNF+/−). We then crossed the BDNF+/− mice with D1-Cre or D2-Cre mice and used AAV-GCAMP6s-FLEX to record neural activity from each of the two subpopulation of cells within the NAc during these mGluR5-PAM induced grooming bouts ($n = 12$ WT / D1-Cre, $n = 13$ BDNF+/− / D1-Cre, $n = 12$ WT / D2-Cre, $n = 10$ BDNF+/− / D2-Cre).

Results: We show that selective BDNF deletion within the mOFC-NAc circuit using the BDNFfl/fl mice leads to an increased amount of time spent grooming ($p < 0.05$, student *t*-test). In BDNF+/− mice, we showed the mGluR5 is expressed at notably higher levels only in the NAc, but not in the OFC ($p < 0.05$, student *t*-test). Lastly, we show that with a single dose of systemic mGluR5 PAM, BDNF+/− mice had similar number of

grooming bouts but had significantly longer average grooming bout length compared to WT mice ($p < 0.01$, student *t*-test). This increase in mGluR5 PAM induced grooming behaviors is also correlated with increase in total NAc neural activity in the BDNF +/− mice with the initiation of the grooming bout, which is also reflected in the neural activity recorded from D1 and D2 subpopulations of the NAc.

Conclusions: These preliminary findings suggest that with the loss of BDNF within the mOFC-NAc circuit, there is a possible compensatory increase in NAc mGluR5 expression. This increased mGluR5 expression and activity may be the molecular mechanism underlying these aberrant grooming behaviors. Our findings provide a potentially novel pharmacological target that may ameliorate these pathological perseverative behaviors commonly seen in those with obsessive-compulsive spectrum disorders.

Keywords: BDNF, mGluR5 Receptors, Nucleus Accumbens, Obsessive-Compulsive Spectrum Disorders (OCDS), Fiber Photometry

Disclosure: Nothing to disclose.

T128. Altered Fronto-Limbic Functional Connectivity Predicts Response to Exposure Response Prevention Therapy in OCD in Pediatric OCD

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Background: The prevailing neurobiological model of OCD proposes that altered functioning of cortico-striato-thalamo-cortical (CSTC) brain circuits underlie obsessive-compulsive symptoms. Evidence from recent research suggest additional alterations outside the CSTC circuits, such as within fronto-limbic circuits. In particular, altered functional connectivity between the basolateral amygdala (BLA) and the ventromedial prefrontal cortex (vmPFC) may be a promising marker of treatment outcome in patients with OCD. Indeed, treatment studies from adults with OCD suggest that BLA-vmPFC resting state functional connectivity (rs-fc) predicts response to Cognitive Behavioral Therapy (CBT) centered on Exposure and Response Prevention (Fullana et al., 2017; Gottlich et al., 2015), the first-line treatment for OCD. No study to date has specifically examined BLA-vmPFC connectivity and whether it can predict treatment response in pediatric OCD.

Methods: Resting state functional magnetic resonance imaging (rsfMRI) scans were acquired from 25 unmedicated, treatment-naïve pediatric OCD patients (12.8 +/− 2.9 years) and 23 age- and sex-matched healthy controls (HCs; 11.0 +/− 3.3 years). Twenty-two of the OCD patients completed a 12 to 16-week course of CBT with E/RP interventions for OCD (March & Mulle, 1998). Participants from both groups were rescanned after the 12-16-week period. OCD symptoms were assessed at baseline and end of treatment using the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS). we used a seed-based approach to examine BLA-vmPFC rs-fc. For each participant, pairwise correlation coefficients of rsfMRI time-series data were computed between BLA and vmPFC at each time point. Analyses of covariance (ANCOVAs) examined group difference in baseline rs-fc. For connections with significant baseline group differences, within-group repeated measures ANCOVAs were conducted to examine whether altered rs-fc in OCD significantly changed after CBT. In patients with OCD, we also used cross-lagged panel modeling to examine relationships between rs-fc and OCD symptoms pre- and post-CBT, allowing us to identify and disentangle directional effects between functional connectivity and OCD symptoms. We hypothesized that BLA–vmPFC rs-fc would be altered in the patients with OCD relative to HC, and change following CBT. We also hypothesized that BLA–vmPFC rs-fc would predict response to CBT and that the magnitude of change in connectivity would associate with the magnitude of symptom change pre- to post-CBT. Given the scarcity of prior rs-fMRI studies in pediatric OCD and heterogeneity in the methods and samples used in previous studies of adults with OCD, we did not formulate specific hypotheses regarding the direction of effects (i.e., decreased or increased rs-fc). Finally, we explored whether effects detected were specific to the BLA–vmPFC pathway or whether it extended to another fronto-amygdalar pathway (i.e. the centromedial amygdala–vmPFC pathway). All analyses adjusted for age, sex, and head motion in the scanner.

Results: Right BLA-vmPFC rs-fc at baseline was significantly reduced (more negative) in patients with OCD relative to HCs ($F(1,43) = 5.822$, $p = 0.020$). In patients with OCD, right BLA–vmPFC rs-fc became significantly more positive following CBT ($F(1,16) = 6.872$, $p = 0.019$).

More positive (less negative) right BLA-vmPFC rs-fc at baseline predicted greater reduction in OCD symptoms post-CBT ($r = -0.330$, $p = 0.018$). However, changes in BLA-vmPFC rs-fc was unassociated with change in OCD symptoms pre- to post-treatment (ps > 0.1). No baseline group differences were detected in CMA–vmPFC rs-fc (all ps > 0.1). Baseline CMA-vmPFC rs-fc did not significantly predict change in OCD symptoms severity from pre- to post-CBT (ps > 0.1).

Conclusions: Using a hypothesis-driven approach, we found altered BLA–vmPFC rs-fc in pediatric OCD that predicted response to, and changed with, CBT. These findings suggest altered BLA-vmPFC rs-fc that predicted response to CBT outcome, partially replicating and extending prior findings from adults (Fullana et al., 2017; Gottlich et al., 2015) for the first time in a pediatric sample of patients with OCD. Both BLA and vmPFC are known to be involved in fear processing, regulation and generalization, as well as in extinction learning, a likely mechanism of action of Exposure and Response Prevention. Thus, the present results provide further evidence of the potential of BLA-vmPFC pathway as a promising target for novel treatments or prevention strategies aimed at facilitating adaptive learning and fear extension in children with OCD or subclinical OC symptoms.

Keywords: Resting-State fMRI, Obsessive-Compulsive Disorder (OCD), Pediatric, CBT, Exposure Therapy

Disclosure: Nothing to disclose.

T129. Examining the Acute Effect of Psilocybin in Treatment-Resistant Obsessive Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is profoundly disabling. It is a complex neuropsychiatric condition characterized by intrusive thoughts, images or urges (obsessions), and repetitive behaviors (compulsions) that are performed to temporarily mitigate the anxiety and discomfort associated with obsessions. OCD is one of the few psychiatric disorders in which invasive brain surgery is an accepted therapeutic option, which is a testament to the profound suffering it can produce. Existing medications can benefit many patients. However, they have a therapeutic lag time of ~3-8 weeks, most treatment responders continue to experience problematic residual symptoms, and upwards of 30% of patients are refractory to available treatments. Novel, more effective, and faster-acting interventions are urgently needed. Recent studies

have reported acute, and sometimes enduring, clinical benefit after a single administration of psilocybin in patients with OCD. The persistence of clinical effects long after intoxication has worn off implies lasting brain changes, but the mechanisms underlying these lasting therapeutic effects remain poorly understood.

Methods: We are conducting the first double-blind, placebo controlled study of psilocybin in OCD (NCT03356483). 6 out of a planned 30 patients with treatment resistant OCD have been randomized to either a single dose of psilocybin (0.25mg/kg) or active placebo (niacin 250mg). Psilocybin is administered in a controlled setting in an inpatient research unit in the presence of two research staff members who provide support during drug administration. Structured psychotherapy is not provided. The primary clinical endpoint is at 48 hours, though we are collecting follow-up data for 3 months. OCD symptoms are measured with the acute Yale-Brown Obsessive-Compulsive Scale (acute-YBOCS). Patients complete two resting-state fMRI scans, one 24 hours before treatment and the second 48 hours after treatment. In addition, we are collecting numerous questionnaires designed to examine how the phenomenology of subjective experiences during psilocybin intoxication relates to clinical changes.

Results: We will present the results of an interim analysis. OCD patients who received psilocybin ($N = 4$) exhibited reductions in acute-YBOCS scores from baseline ($M = 25.5$, ranging from 18 to 29) to 48-hours ($M = 15$, $SD = 11.52$,) after drug administration (1-tailed within-subject *t*-test: $t(3) = 2.71$; $p = 0.036$). Among the OCD patients who received placebo (niacin) ($N = 2$), acute-YBOCS scores minimally changed from baseline ($M = 25.5$) to 48-hours ($M = 23.5$) after drug administration. Paired *t*-tests could not be completed for this group due to small sample size. The patients ($N = 2$) who were randomized to placebo returned two weeks later to receive open-label placebo; both had robust and enduring clinical responses.

Conclusions: This study builds on previous work identifying psilocybin as a potential treatment for patients with OCD, as well as in mood and anxiety disorders. We report here encouraging preliminary results from the first blinded, placebo-controlled study of single-dose psilocybin in treatment-resistant OCD. At the time of the poster presentation, we anticipate presenting data from additional subjects.

Keywords: Obsessive-Compulsive Disorder (OCD), Psilocybin, Psychedelics

Disclosure: Nothing to disclose.

T130. Persistent Avoidance is Gated by Insular-Orbital Inputs to the Prelimbic Cortex

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Background: A common symptom of obsessive-compulsive disorder (OCD) is the persistent avoidance of cues that have been associated with a negative outcome. This maladaptation becomes evident as the subjects fail to respond to standard treatments such as exposure-with-response prevention (ERP) therapy. While previous studies have highlighted the role of the insular-orbital cortex in fine-tuning avoidance-based decisions, limited evidence about its influence on other key prefrontal areas in gating avoidance behavior is available.

Methods: To model persistent avoidance and ERP in rats, we used the platform-mediated avoidance (PMA) task followed by extinction-with-response prevention (Ext-RP) training. These behavioral paradigms were combined with optogenetic and single unit recordings to characterize the role of the anterior insular and lateral orbitofrontal cortex (AI/LO) projections on avoidance expression and extinction, respectively. During PMA, rats were conditioned during 8 or 20 (overtrained) days to avoid a tone-signaled shock by stepping onto a nearby platform at the cost of receiving reward (sugar pellets) followed by optogenetic manipulations at post conditioning test. Subsequently, all the rats underwent 4 days of Ext-RP training, where the tone-shock association was extinguished while access to the platform was blocked with a barrier. This was followed by a post Ext-RP test (no barrier), with optogenetic manipulations.

Results: Using anatomical tracing analyses, we first found that AI/LO inputs predominantly target the rostral portion of the prelimbic cortex (rPL). Thus, photo-silencing AI/LO terminals in rPL induced persistent avoidance during post Ext-RP test, an effect that was remarkably maintained seven days later in the absence of laser. Consistent with this, photo-activation of the AI/LO-rPL projection reduced persistent avoidance at test (post Ext-RP). There was no effect of photo-silencing AI/LO projections to ventral striatum or basolateral amygdala on avoidance, highlighting the specificity of the AI/LO-rPL projection in gating maladaptive avoidance behavior. Single unit recordings revealed that photo-silencing the AI/LO terminals in rPL decreases the firing rate of this region, suggesting that AI/LO drives activation in rPL to overcome persistent avoidance.

Conclusions: Our findings suggest that the activation of inputs from AI/LO to rPL can prevent persistent avoidance and facilitate the transfer of extinction learning to avoidance behavior at a key decision point. Also, AI/LO to rPL may be homologous to vlPFC and dACC in humans, suggesting deficient activity in this pathway in OCD and a new target for transcranial stimulation.

Keywords: OCD, Orbitofrontal Cortex (OFC), Insular Cortex, Prelimbic Cortex, Persistent Avoidance

Disclosure: Nothing to disclose.

T131. ProcessGenesList: A Novel Approach to Link MicroRNA Expression and Human Brain Imaging: Application to Borderline Personality Disorder

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Background: Individual microRNAs (miR) can affect the expression levels of hundreds of genes, both in the cell in which they are synthesized, and in the case of circulating miR, in distant locations. Thus, it is possible that miR associated with a specific disorder or phenotype affect brain-expressed genes in specific regions. We developed ProcessGenesList (PGL) to assess where in the brain are groups of genes co-expressed the most. Since miR-124 shows altered expression in borderline personality disorder (BPD) we studied its modulated genes with PGL to find possible brain regions associated with BPD and modulated by the effect of miR-124.

Methods: Genes possibly modulated by miR-124 (previously shown to be altered in BPD, Prados et al Genes Brain Behav 2015) were recovered from online databases. PGL was run on those genes to obtain a list of brain regions in which those genes are co-expressed the most. The region(s) with highest PGL score were then used in a Freesurfer volumetry study to compare patients with ($N = 111$, adult, both sexes) and patients without ($N = 111$, adult, both sexes) BPD from The Menninger Clinic in Houston, TX).

Results: A total of 1222 genes were found to be possibly modulated by miR-124. PGL (using normalized gene expression levels from the Allen Brain Atlas) found that the brain region with highest co-expression of those genes was the left globus pallidus.

We next compared the volume of the left globus pallidus (normalized by total intracranial volume) between patients with and without BPD. BPD patients had smaller left globus pallidus than patient controls (normalized volume, CONTROL = 100 +/− 0.8; BPD = 97.3 +/− 0.9; $P = 0.026$).

Conclusions: Despite the fact that the difference in left globus pallidus volume was small, it was statistically significant and may be clinically relevant. We showed that by studying the averaged gene expression in the brain of genes possibly associated with an altered miR, we obtained a single hypothesis to be studied using brain imaging (other regions with lower PGL score will be exploratorily studied). By decreasing the brain imaging multiple comparison problem, we were able to find a statistically significant difference in brain morphometry between two populations of patients.

Keywords: Borderline Personality Disorder, MicroRNA, Globus Pallidus, FreeSurfer

Disclosure: Nothing to disclose.

T132. Cell-Type Specific Type 1 Cannabinoid Receptor Distribution Across the Human and Non-Human Primate Cortex

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Background: Alterations in type 1 cannabinoid (CB1) receptor are implicated in psychiatric disorders such as schizophrenia. CB1 participates in both depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE), suggesting its involvement in both inhibitory and excitatory circuits. However, previous studies describing the distribution of CB1 in human and non-human primate cortex utilized antibodies that preferentially target CB1 at inhibitory boutons. Given CB1's role in both DSI and DSE, understanding cell-type specific CB1 distribution may increase our insight into its regulation of excitatory-inhibitory balance. Here, we investigate CB1 distribution in both inhibitory and excitatory boutons using quantitative fluorescent microscopy.

Methods: Coronal sections containing dorsolateral prefrontal cortex (DLPFC), superior temporal gyrus (STG), and hippocampus from adult male macaques and humans are labeled with antibodies for CB1 (validated to target both excitatory and inhibitory boutons), VGLUT1 (labeling intracortical excitatory boutons), and VGAT (labeling intracortical inhibitory boutons). Samples are imaged to visualize protein expression patterns within cortical regions and layers. Fluorescent intensities of CB1 label within boutons of each type are obtained for analysis.

Results: CB1 co-expression with both VGLUT1 and VGAT are visualized in axons and boutons in all three brain regions in both non-human primate and human samples. CB1 fluorescent intensity is lower in excitatory boutons compared to inhibitory boutons, and exhibits distinct patterns within each brain region and cortical layer.

Conclusions: Previous studies describing the distribution of CB1 in human and non-human primate cortex utilized antibodies preferentially targeting CB1 at inhibitory boutons. Using a CB1 antibody that targets both excitatory and inhibitory boutons, we demonstrate distinct cell-type specific regional and laminar distributions of CB1 in the human and non-human primate cortex. This may increase our understanding of how CB1 differentially regulates excitatory-inhibitory balance within these areas. Expanding upon these findings, we plan to evaluate cell-type specific CB1 alterations in schizophrenia as a potential contributor to the functional disturbances seen in this disorder.

Keywords: Psychosis, Endocannabinoid System, Excitation-Inhibition Balance

Disclosure: Nothing to disclose.

T133. Effects of Repetitive Transcranial Magnetic Stimulation on Brain Structure in Schizophrenia: Data From a Double-Blind, Randomized, Sham-Controlled Trial

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Background: Repetitive transcranial magnetic stimulation (rTMS) has been demonstrated to have efficacy for the treatment of major depressive disorder. Furthermore, pilot studies showed that rTMS to the dorsolateral prefrontal cortex (DLPFC) improves working memory impairment in schizophrenia. Yet, the effect of rTMS treatment on brain structure is poorly understood. The DLPFC plays a critical role in working memory performance. Therefore, measuring the effects of rTMS on the DLPFC, and its connections, can provide important insight into the effects of rTMS on brain structure, and advance our understanding of potential mechanisms of efficacy. In this study, we aimed to assess whether four weeks of rTMS treatment bilaterally to the DLPFC in patients with schizophrenia changes grey matter structure in DLPFC (i.e. DLPFC thickness) and white matter connections important for working memory performance (fractional anisotropy (FA) of the genu of the corpus callosum (gCC; connecting left and right DLPFC) and of the left superior longitudinal fasciculus (SLF; connecting DLPFC to parietal cortex)) using a double-blind, randomized, sham-controlled study design.

Methods: This double-blinded, parallel, sham-controlled study (NCT01880255) randomized 81 participants to active vs. sham rTMS administered five days/week for four weeks (20 sessions). We enrolled clinically stable (no change in antipsychotic medication or dosage for at least four weeks prior to randomization) patients (male and female, age 18-59) with a diagnosis of schizophrenia or schizoaffective disorder. Active stimulation was delivered at 90% resting motor threshold intensity using 25 stimulation trains of 30 stimuli each (750 pulses total) at 20 Hz, consistent with our pilot study (Barr et al., 2013). Participants completed an MRI as well as clinical and cognitive assessments directly before and after receiving rTMS. Following quality control, high quality MRI data was available from 59 participants who completed both pre- and post-scans obtained on a 3T GE scanner at CAMH. T1-weighted images were automatically processed with the longitudinal stream in FreeSurfer (v.6.0), a within-subject template estimation for unbiased, reliable, longitudinal analysis, to obtain vertex-wise cortical thickness measures. Cortical regions of interest (ROIs) were parcellated using the Human Connectome Project's Multi-modal Cortical Parcellation. The DLPFC ROI closest to the stimulation site was identified for every participant using Euclidean distance and corresponded to the atlas ROI p9-46v on the left and right hemisphere. Diffusion-weighted imaging data (60 gradient directions with b=1000 and 5 b=0 scans) was preprocessed (denoising, correction for motion, eddy currents and susceptibility-derived distortions) before fitting the tensors. White matter microstructure (i.e. FA) was measured from the diffusion tensor imaging (DTI) skeleton generated using Tract-Based Spatial Statistics (TBSS). FA was extracted from the gCC and left SLF white matter ROIs using the JHU atlas. Statistical analyses were conducted in R. Linear regressions were used for the pre-post analyses including covariates of age, sex, the baseline outcome measure (i.e. DLPFC thickness or FA at baseline) and days between MRI scans. With four pre-specified imaging measures, an alpha=0.0125 was

considered significant. Pre-specified associations between change in brain structure and change in symptoms/cognitive measures were also explored using Pearson's correlation analysis.

Results: We observed a significant effect of treatment group on change in right DLPFC thickness (ß = −0.04, Std. Error = 0.01, t = −2.6, $p = 0.01$), whereby the active group experienced a larger increase in thickness than the sham group. There was no effect of treatment group on change in left DLPFC thickness (ß = −0.01, Std. Error = 0.02, t = −0.66, $p = 0.51$). We did not observe any effect of treatment group on change in FA in the pre-specified ROIs (gCC: ß = −0.001, Std. Error = 0.003, t = −0.49, $p = 0.63$; left SLF: ß = −0.002, Std.Error = 0.002, t = −0.95, $p = 0.35$). The exploratory analysis did not show association of cortical thickness change with changes in working memory performance, general cognition, or negative symptoms. However, improvement in depressive symptoms, measured with the Calgary Depression Scale for Schizophrenia (CDSS), showed association with increase in right DLPFC thickness in the active group (active groups: $r = -0.47$, $p = 0.008$; sham group: $r = -0.04$, $p = 0.8$).

Conclusions: Our findings of an increase in right DLPFC thickness together with a decrease in depressive symptoms are novel and open an important new avenue of treatment given the lack of efficacy of antidepressant medications in schizophrenia.

Keywords: Non-Invasive Brain Stimulation, Cortical Thickness, Dorsolateral Prefrontal Cortex, Schizophrenia - Novel Treatment, Non-Pharmacological Interventions

Disclosure: Nothing to disclose.

T134. Efficacy and Safety of BI 425809 Once Daily in Patients With Schizophrenia: Top-Line Phase II Results

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Background: BI 425809, a selective glycine transporter 1 (GlyT1) inhibitor, may improve cognitive impairment in patients with schizophrenia. Here we present the top-line results from a proof-of-concept study assessing the efficacy and safety of BI 425809 vs placebo.

Methods: This Phase II, double-blind, placebo-controlled, parallel-group study recruited adults (18–50 years) with schizophrenia. Eligible patients were randomised to an oral dose of BI 425809 (2, 5, 10 or 25 mg) or placebo (plus standard of care), in a 1:1:1:1:2 ratio once daily, for 12 weeks. The primary endpoint was the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) overall composite T-score. The Schizophrenia Cognition Rating Scale (SCoRS) total interviewer score was assessed as a secondary endpoint. Further endpoints included the Positive and Negative Syndrome Scale (PANSS) total score and PANSS negative score at Week 12. Safety was also assessed. Primary analyses of MCCB and SCoRS was performed using a multiple comparison procedure and modelling approach combined with mixed-effects model repeated measures (MMRM). PANSS total and PANSS negative scores were evaluated using a MMRM for point estimates and the corresponding 95% confidence intervals for pairwise treatment comparisons.

Results: 509 patients from 81 centres across 11 countries worldwide were randomised and 444/509 (87.2%) completed the 12-week treatment period. Analyses of the primary endpoint showed statistically significant evidence for a non-flat dose response relationship across the doses investigated in favour of BI 425809 (one-sided $p < 0.05$). Secondary analyses of the primary endpoint showed improvements in change from baseline to Week 12 at BI 425809 10 and 25 mg vs placebo (MCCB overall, nominal p-values: 0.0122 and 0.0287). SCoRS, PANSS total and PANSS negative scores showed no differences in favour of BI 425809 at any dose. BI 425809 was well tolerated.

Conclusions: Proof-of-concept was established with improvements in cognition observed at BI 425809 10 and 25 mg.

Acknowledgements: The authors would like to thank Jay Eui Soh for his contributions to the statistical analyses of the data.

Funding: Boehringer Ingelheim International GmbH (NCT02832037; 1346-0009)

Keywords: Schizophrenia, BI 425809, Cognitive Impairment

Disclosure: Boehringer Ingelheim: Employee (Self)

T135. Assessing the Utility of Electroencephalography as a Clinical Biomarker in a BI 425809 Phase II Substudy in Patients With Schizophrenia

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Background: Patients with schizophrenia exhibit a diminished pre-attentive sensation response to deviating auditory stimuli and a reduced auditory steady-state response (ASSR), detectable by electroencephalography (EEG). As part of a Phase II trial investigating the efficacy and safety of the novel glycine transporter 1 (GlyT1) inhibitor BI 425809 in patients with schizophrenia, this substudy evaluated various EEG parameters as potential diagnostic, predictive or treatment response biomarkers. Objectives were to gain insight on EEG methodologies, neurophysiological changes in schizophrenia, and the influence of treatment on these measures.

Methods: The Phase II, double-blind, placebo-controlled, parallel-group study (NCT02832037) recruited adult patients (18–50 years of age) with schizophrenia. Eligible patients were randomized to an oral dose of BI 425809 (2, 5, 10, or 25 mg) or placebo (plus standard of care), in a 1:1:1:1:2 ratio once daily, for 12 weeks. EEG measurements were made at two different time points, once in the 14-day period before the main study (baseline) and again in the 7-day period before the end of the trial (Week 12). EEG assessments included resting-state EEG (qEEG) to assess resting brain activity and any correlation with cognitive functions/states; mismatch negativity (MMN) to assess pre-attentive sensation of deviating auditory stimuli; and ASSR. The outcome of EEG assessments at baseline and their change from baseline were compared with clinical assessments from the same trial visits, including Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), the Schizophrenia Cognition Rating Scale (SCoRS), and the Positive and Negative Syndrome Scale (PANSS). These analyses aimed to provide insight into the potential of EEG parameters to serve as diagnostic, predictive, or treatment response markers. Furthermore, the quality of EEG assessments and data processing were evaluated for future optimization.

Results: Overall, 79 patients from 17 sites in the USA and EU (Germany, Italy, Poland, UK) were randomized into the EEG substudy (BI 425809 2 mg, $n = 14$; 5 mg, $n = 10$; 10 mg, $n = 20$; 25 mg, $n = 15$; placebo, $n = 20$). Twenty-two patients were not evaluated due to missing follow-up or low-quality data. Thus, 57 patients completed the substudy and their samples were evaluated regarding their utility as a biomarker for diagnostic, predictive, and treatment responses. Compared with the full analysis set of the parent study, there were more males (77% vs

65%), European (51% vs 30%), and African American (33% vs 24%) patients, and more patients who were current smokers (56% vs 42%) in the EEG substudy. Mean baseline MCCB, SCoRS and PANSS data were similar (MCCB overall composite score, 30.3 vs 31.5; SCoRS total score, 36.9 vs 36.4; PANSS total score, 60.1 vs 60.8) between substudy and parent study, respectively. High variability of the EEG parameters was observed. Correlation of the EEG parameters (qEEG, MMN, and ASSR) at baseline with the clinical scores (MCCB composite, SCoRS, and PANSS total scores) will be presented.

Conclusions: In this multicenter substudy in patients with schizophrenia, the association of EEG parameters with clinical scores at baseline supports the use of EEG as a diagnostic marker; however, due to the high variability observed in the EEG data, the clinical relevance of its use is limited. The baseline EEG variability may, at least in part, be due to the involvement of multiple sites with different levels of EEG expertise. Restricting EEG assessment to fewer, high-quality sites, with a minimum number of patients, could reduce inter-site variability providing more robust data to inform on the value of EEG in supporting clinical drug development. Additionally, correlation of EEG assessments from end of treatment visit with clinical scores may yield information on the potential of EEG as a predictive or treatment response biomarker.

Funding: Boehringer Ingelheim International GmbH (NCT02832037)

Keywords: Electroencephalography, Schizophrenia, BI 425809, Glycine transporter 1 inhibitor

Disclosure: Boehringer Ingelheim: Employee (Self)

T136. ADVANCE: Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Adjunctive Pimavanserin in Patients With Negative Symptoms of Schizophrenia

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Background: Approximately 50% of patients with schizophrenia experience negative symptoms, which are associated with reduced quality of life, poor social functioning, and long-term disability. Pimavanserin is a selective, 5-hydroxytryptamine (5-HT) 2A inverse agonist/antagonist with lower activity at 5-HT2C receptors, and no affinity for adrenergic, dopaminergic, histaminergic or muscarinic receptors. Previous studies have shown beneficial effects of adjunctive pimavanserin in patients with schizophrenia including significant improvement of negative symptoms. ADVANCE evaluated the effects of adjunctive pimavanserin on negative symptoms of schizophrenia.

Methods: This was a phase 2, 26-week, randomised, double-blind, placebo-controlled study of stable outpatients with predominant negative symptoms from Europe and North America. Eligible patients had Positive and Negative Syndrome Scale (PANSS) Marder negative factor score ≥20 at screening and baseline, and ≥4 on at least 3, or ≥5 on at least 2 of these negative symptom items. A Marder positive factor score ≤22, no score ≥5 and a score of 4 on no more than 2 of P1, P3 or P6 items was also required. Patients were randomised to pimavanserin or placebo added to main antipsychotic therapy. The initial dose was 20 mg once daily, with dose adjustments allowed to 34 mg or 10 mg until Week (W) 8. The primary endpoint was change from baseline to W26 on the Negative Symptom Assessment-16 (NSA-16) total score. The key secondary endpoint was change from baseline to W26 on the Personal and Social Performance scale. Safety and tolerability were also assessed. The change from baseline in NSA-16 total score was analysed using mixed model repeated measures, and treatment difference (least squares [LS] mean) at W26 was tested at an alpha level of 0.05 (2-sided).

Results: Of 403 patients randomised (400 patients included in efficacy analysis [201 placebo; 199 pimavanserin]), 87.8% were from European sites. The final pimavanserin dose was 34 mg in 53.8%, 20 mg in 44.7% and 10 mg in 1.5% of patients. Significant improvement vs placebo was observed for the NSA-16 total score at 26 weeks with pimavanserin (LS mean: −10.4 vs −8.5, $p = 0.043$, effect size: 0.21). Improvement vs placebo was greater in patients ($n = 107$) whose last dose level of pimavanserin was 34 mg (LS mean: −11.6 vs −8.5, unadjusted $p = 0.0065$, effect size: 0.34). No significant difference was observed for the key secondary endpoint. The incidence of any adverse event (AE) was 35.1% with placebo and 39.8% with pimavanserin. The most common AEs were headache (5.0% and 6.5%) and somnolence (5.0% and 5.5%) with placebo and pimavanserin, respectively. Serious AEs occurred in 0.5% (placebo) and 2.0% of patients (pimavanserin), and AEs leading to discontinuation occurred in 3.0% (placebo) and 5.0% (pimavanserin). No clinically relevant effects were observed with pimavanserin for vital signs, weight, metabolic parameters or extrapyramidal symptoms.

Conclusions: Negative symptoms improved significantly with pimavanserin vs placebo in stable patients with predominant negative symptoms of schizophrenia. Greater improvement was observed at a 34-mg dose. The tolerability profile of pimavanserin was comparable to placebo with similar incidence rates of adverse events.

Keywords: Schizophrenia, Negative Symptoms, Pimavanserin, Randomized Clinical Trial

Disclosure: ACADIA Pharmaceuticals Inc: Employee (Self)

T137. Efficacy of Add-On Sulforaphane for Improving Cognition and Symptoms in Frist-Episode Schizophrenia: A Randomized Double-Blind Study

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Background: Cognitive symptoms are common and associated with significant dysfunction in schizophrenia. Oxidative stress, inflammation and epigenetic modifications involving HDAC and methylating enzymes have been implicated in some of the risk factors or underlying pathophysiology of schizophrenia. Sulforaphane has chemical properties both as an antioxidant and an HDAC inhibitor. One published study suggests it have beneficial effects in autism. Studies in PCP animal models suggest it may be effective on improving some of the cognitive deficits and underlying pathophysiological abnormalities in schizophrenia. However, no large sample trials have been done to examine the efficacy of sulforaphane in treating cognitive and psychotic symptoms in schizophrenia. The objective of the current study was to determine the efficacy and safety of sulforaphane as an add-on treatment for patients with first episode schizophrenia and particularly its effects on cognitive symptoms.

Methods: This double-blind randomized trial was conducted from November 2016 to June 2019 in 4 psychiatric institutions in China. Patients, male and female, with first-episode schizophrenia with minimum PANSS >75 were enrolled and followed for 22 weeks. (ClinicalTrials.gov: NCT02880462). The patients were randomized to 3 groups (low and high doses of sulforaphane vs placebo) and symptomatic and cognitive assessments were done at multiple time points. The Avmacol® tables contained glucoraphanin and active myrosinase which

converted to sulforaphane with the estimated delivery of approximately 48 and 72 umol of sulforaphane daily in the low and high dose group. The primary outcome was change in the MATRICS Composite score and secondary outcome changes in MATRICS Domain scores. Additional secondary outcomes were change PANNS Total score PANSS 5-factor scores, and change in side-effect scales scores. The main statistical analysis was intent to treat mixed model analysis

Results: A total of 172 patients with first-episode of schizophrenia were enrolled and randomized into 3 study groups and 151 patients had at least 1 follow up evaluation. In the mixed -model intention-to-treat analysis, sulforaphane significantly improved performance scores on several Domains of the MATRICS battery, spatial working memory ($P = 0.004$), reasoning-problem solving ($P = 0.063$), and verbal learning ($P = 0.031$) (Overall effect sizes $d = 0.26–0.35$) It did not improve global cognitive function as measured by the MATRICS overall composite score. There were no effects on PANSS symptom scores. Sulforaphane was well tolerated and side effects were very low and infrequent. In a sub-sample of subjects in whom GSH and GSSG were measured at baseline and after 4 weeks of study drug; the ratio of GSH/GSSG increased significantly more in the sulforaphane than placebo patients ($P = 0.027$), an indicator or less oxidative stress in the sulforaphane treated subjects.

Conclusions: If these positive effects of sulforaphane on selected aspects of cognitive function in schizophrenia can be replicated, it may be useful as an add-on treatment for reducing cognitive deficits in schizophrenia.

Keywords: Sulforapahne, Schizophrenia Novel Treatment, MATRICS Consensus Cognition Battery (MCCB), Visuospatial Working Memory, Verbal Learning

Disclosure: Nothing to disclose.

T138. Increased Repulsion of Visual Working Memory Representations in Schizophrenia

Abstract not included.

T139. Domestic Mass Shooters and Terrorists: Prevalence of Untreated Psychiatric Illness

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Background: A critical question that has evaded scientific study is whether the behavior of domestic mass shooters is associated with underlying medical or psychiatric illness. In contrast to past anecdotal reconstructions from the media, we conducted the first systematic, scientific study of mass killers to determine the diagnosis, possible treatment, and prevalence of psychiatric illness.

Methods: Our subjects were selected from a database of 115 mass shootings – defined by four or more deaths—in the United States between 1982 and 2019 to study retrospectively 55 shooters. We developed a questionnaire, focused on pre-shooting life history, symptoms, presence or absence of psychiatric illness and any history of treatment. A research psychiatrist interviewed the forensic psychiatrist and reviewed the judicial records. We were able to get data on thirty-five cases in which the assailant survived the crime as well as twenty cases in which the assailant died at the time of the crime.

Results: Of thirty-five cases in which the assailant survivor, there was insufficient information to make a diagnosis in three cases. In the remaining 32 cases, 18 (56%) had schizophrenia, 1 bipolar disorder, 1 delusional disorder, and 3 with severe personality disorder, 1 of which also had substance use disorder. 9 had no psychiatric disorder.

Of the 20 cases where the assailant was killed, in 5 cases there was insufficient information, from the remaining 15, 8 (53%) had schizophrenia, 1 paranoid personality disorder, and 6 had no disorder that we could discern.

None of those with psychiatric illness were medicated.

Conclusions: Although we found a correlation between domestic mass shooters and undiagnosed and untreated schizophrenia, further research is necessary to determine the role of psychiatric illness in criminal conduct and whether psychiatric treatment might help in preventing these tragedies

Keywords: Schizophrenia (SCZ), Psychotropic Medications, Violence

Disclosure: Nothing to disclose.

T140. Genome-Wide Association Study of Suicidal Behaviors Among US Veterans With Schizophrenia or Bipolar Disorder

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Background: Severe mental illness (SMI) is a serious problem in veterans, with increased risk for self-injurious behavior, suicidal ideation and suicide attempt (SIB) and suicide completion. Previous research has suggested genetic influences on SIB, both among SMI patients and the general population. We examined genomic correlates of SIB in 8,049 male and 1,290 female veterans with schizophrenia or bipolar disorder.

Methods: Self-reported SIB, combined into a single latent trait, were assessed with the Columbia Suicide Severity Rating Scale (lifetime version). Following quality control procedures and ancestry inferences, 4,012 European Americans (EAs) (3,223 attempters) and 2,651 African Americans (AAs) (1,955 attempters) were identified. We performed a genome-wide association study (GWAS) of SIB and used METAL to perform fixed-effects meta-analysis with published Psychiatric Genomics Consortium (PGC) findings. We applied GNOVA, a framework to estimate genetic overlap with 2,626 traits from the UK Biobank (UKB).

Results: Among EA participants with a diagnosis of bipolar disorder, we identified a novel genome-wide association upstream of MIR572 at 4p16; intriguingly, fluoxetine increases expression of. combining data from CSP #572 and PGC, we identified a second novel genome-wide significant association with SNPs in CDH11 at 16q21, which encodes a class two cadherin molecule that plays a critical role in cortical development; CDH11 been implicated in substance-abuse behaviors, autism, and depression. Our meta-analysis generated additional support for MIR548AJ2 at 4p15.2, a locus that has yielded evidence of pleiotropic effects on cognitive ability, years of education and schizophrenia. Estimated genetic covariances between SIB and 3 UKB traits survived false discovery rate correction: depression and tenseness in the past two weeks, and miserableness. Polygenic scores constructed from PGC and UKB results for suicide attempt were nominally associated with SIB.

Conclusions: Our novel GWAS meta-analyses yielded three genome-wide significant findings for SIB, including novel associations with variants in MIR572 and CDH11. Polygenic scoring and genetic correlations with UKB traits support a complex architecture for SIB and the commonality of their genomic risk factors across SMI and the general population.

Keywords: Schizophrenia and Bipolar Disorders, Suicidal Behavior, Suicidal Ideation, Non-Suicidal Self-Injurious Behavior, Genome-Wide Association Studies

Disclosure: Nothing to disclose.

T141. Transcription and Translation Regulated by microRNA in Human Brain and its Potential Contribution to Psychiatric Disorders

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Background: Regulation of gene expression and translation is critical for maintaining normal brain functions. Dysregulation is associated with brain disorders. MicroRNAs (miRNAs) are a group of small non-coding RNAs, which post-transcriptionally regulate mRNAs abundance and repress their translation. Though miRNA regulation on mRNA expression in the human brain has been explored, how miRNA regulates targets at translation level and how the translational regulation compares with mRNA regulation, the contribution of these two regulations to genetic risk of psychiatric disorders have not been well studied yet.

Methods: We performed miRNA-seq ($n = 289$), mRNA-seq ($n = 417$), and ribo-seq ($n = 211$) of the dorsolateral prefrontal cortex from controls and individuals with schizophrenia (SCZ) and bipolar disorder (BD). Based on validated targets and predicted targets for profiled miRNAs from published databases, we examined correlations between miRNA expression and their corresponding target genes' expression at both transcription level by RNA-seq data and translation level by Ribo-seq data. We also tested for the buffer effect of miRNAs by the correlation test between miRNA expression levels and expression variations of target genes. Bipartite and coexpression networks methods identified miRNA-gene interaction modules, followed by analyses of cell specificity and disease associations. We also identified miRNAs perturbed in SCZ and BD by differential expression analyses.

Results: 1) We found that 67% and 55% of miRNA-mRNA target pairs have negative correlation at mRNA level and translation level ($p < 0.05$). The averaged absolute values of miRNA-target correlation coefficients are around 0.2 for both transcription and translation. The significant miRNA-mRNA target pairs had poor overlaps between transcription ($n = 240{,}880$) and translation ($n = 228395$) level (prop of overlaps = 11%). But 76% of the overlapped pairs have a consistent direction of correlation and are enriched for neuronal functions. 2) We found that the targets of miRNA had a lower variation of expression across samples at transcription level ($p = 8.8e\text{-}15$), especially for highly-expressed targets, than the genes that are not miRNA targets, but the difference is small (0.29 vs 0.32). We did not observe such differences of target vs non-target variation at the translation level. 3) We identified 50 and 51 miRNA coexpression modules at transcription and translation levels, which are well preserved. We annotated modules with neural marker genes and neuron-specific miRNAs. 4) We identified five modules that enriched for risk genetic signals including de novo mutation, copy number variants, GWAS signals, and differentially expressed genes for SCZ, BD, and autism.

Conclusions: Over half of miRNAs represses transcription and translation in the human brain, but they may not target the same genes. Such negative regulation is enriched in neurons. miRNAs have a weak buffer effect on the expression of their target mRNA. The buffer effect is less obvious at the translational level. miRNAs maybe have dual functions in regulating cell type-specific genes. The mechanism of positive correlation is not known. miRNA-mRNA coexpression modules contain genetic risk factors of psychiatric diseases.

Keywords: Transcriptome, Schizophrenia (SCZ), MicroRNA, Dysregulation, Bipolar Disorder

Disclosure: Nothing to disclose.

T142. Molecular Pathways Underlying Schizophrenia

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Background: The molecular pathophysiological mechanisms underlying schizophrenia have remained unknown, and no treatment exists for primary prevention. Studies using stem cell-derived neurons have investigated differentially expressed genes (DEGs) and GO and KEGG pathways between patients and controls, but not analyzed data-driven causal molecular pathways involved [Brennand et al. Modelling schizophrenia using human induced pluripotent stem cells. Nature 2011;473:221-225; Tiihonen et al. Sex-specific transcriptional and proteomic signatures in schizophrenia. Nat Commun 2019;10:3933].

Methods: We used Ingenuity Pathway Analysis (IPA) to analyze canonical and causal pathways in two different datasets (total N of subjects = 37), including patients from Finland [Tiihonen et al. Sex-specific transcriptional and proteomic signatures in schizophrenia. Nat Commun 2019;10:3933] and USA [Hoffman et al. Transcriptional signatures of schizophrenia in hiPSC-derived NPCs and neurons are concordant with post-mortem adult brains. Nat Commun 2017;8:2225]. We also used Finnish nation-wide databases ($N = 61{,}889$ for total cohort, $N = 8{,}342$ for incident cohort of first-episode patients) to study the risk of schizophrenia relapse during use of medication found to be a master regulator for a causal IPA pathway. To eliminate selection bias, we used within-individual analysis, also used in several previous studies. As individuals act as their own control, time-invariant covariates are automatically controlled for in the study design. The model was adjusted for time-varying covariates, which included the use of antipsychotics, mood stabilizers, benzodiazepines and antidepressants, the temporal order of treatments, and time since the cohort entry date.

Results: The most significant findings in canonical pathway analysis were observed for glutamate receptor signaling, hepatic fibrosis, and glycoprotein 6 (GP6) pathways in the Finnish dataset, and GP6 and hepatic fibrosis pathways in the US dataset. In data-driven causal pathways, ADCYAP1, ADAMTS, and CACNA genes were involved in the majority of the top 10 pathways differentiating patients and controls in both Finnish (all p-values $< 1.5 \times 10^{-8}$) and US datasets (all p-values $< 1.9 \times 10^{-6}$), but no dopamine-specific genes were consistently involved. Results from Finnish nation-wide databases showed that the risk of schizophrenia relapse was 41% (95% CI 14%–60%) lower among first-episode patients during the use of losartan, the master regulator of a ADCYAP1, ADAMTS, and CACNA –related pathway, compared to those time periods when the same individual did not use the drug. The results for thiazide diuretics, used for the same somatic indication (hypertonia), indicated that the findings were not attributable to general adherence to drug treatments. Antipsychotic use was associated with only slightly lower (46% vs. 41%) risk of relapse than losartan use, and no beneficial outcome was observed for benzodiazepine use.

Conclusions: The results from two independent datasets suggest that the GP6 signaling pathway, and the ADCYAP1, ADAMTS, and CACNA -related pathways are primary

pathophysiological alterations in schizophrenia among patients with European ancestry. While no reproducible dopaminergic alterations were observed, the results imply that agents such as losartan, and ADCYAP1/PACAP -deficit alleviators, such as metabotropic glutamate 2/3 agonist MGS0028 and 5-HT7 antagonists – which have shown beneficial effects in an experimental Adcyap1−/− mouse model for schizophrenia [Ago et al. The selective metabotropic glutamate 2/3 receptor agonist MGS0028 reverses psychomotor abnormalities and recognition memory deficits in mice lacking the pituitary adenylate cyclase-activating polypeptide. Behav Pharmacol 2013;2474-77; Tajiri et al. Serotonin 5-HT(7) receptor blockade reverses behavioral abnormalities in PACAP-deficient mice and receptor activation promotes neurite extension in primary embryonic hippocampal neurons: therapeutic implications for psychiatric disorders. J Mol Neurosci 2012;48:473-481] – could be potential treatments before the full manifestation of illness involving dopaminergic abnormalities.

Keywords: Stem Cells, Pathways, RNA Sequencing, Schizophrenia- Novel Treatment

Disclosure: Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka, Evidera, Sunovion: Honoraria (Self); Eli Lilly, Janssen-Cilag: Grant (Self)

T143. Meta-Analytic Evidence for Reduced Prefrontal Glutamate in Schizophrenia and the Impact of Measurement Quality Metrics

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Background: Alterations in prefrontal glutamatergic signaling are hypothesized to be a key feature of schizophrenia (SZ). Findings from previous meta-analyses of magnetic resonance spectroscopy (MRS) studies, however, have been inconsistent in regard to differences in PFC glutamate in the illness. Since the most recent comprehensive meta-analysis was conducted in 2015, technical methods for MRS studies of glutamate have improved, potentially increasing the power of the technique to detect reliable group differences. Here we conducted an updated meta-analysis of prefrontal MRS studies of glutamate in SZ.

Methods: We conducted an inverse variance weighted, random effects meta-analysis of MRS studies published through March 25, 2020 that measured glutamate in the medial prefrontal cortex (mPFC) or dorsolateral prefrontal cortex (DLPFC) and included both a healthy control (HC) group and group with diagnosed SZ spectrum disorders. Studies were excluded for being an intervention study with no baseline, having MRS scanning performed during a task, participant overlap, not using an internal reference (water or creatine), or not acquiring single-voxel, 1-D spectral data. One additional study was excluded for having an extreme sex ratio imbalance between groups. Metrics sensitive to the quality of the glutamate measurements were used to partition the studies. These included the mean Cramer-Rao lower bound (CRLB) values and mean coefficient of variation (COV) of the reported glutamate values in the patient and control groups.

Results: We identified 36 pairs of HC-SZ independent samples that measured mPFC glutamate and 8 that measured DLPFC glutamate. Significantly reduced mPFC glutamate was observed in the SZ group (Hedges' g $= -0.19$, 95% CI $= -0.32$ to -0.07, $p = 0.003$). Qualitatively, study effect sizes increased as CRLB and COV values decreased. For example, when restricting the meta-analysis to the 14 studies with the lowest mean COV values, Hedges' g was -0.39 (95% CI $= -0.52$ to -0.25, $p < 0.0001$). A similar pattern was observed for the DLPFC. In addition, recent onset SZ tended to show a greater reduction in mPFC glutamate compared to chronic SZ, and this effect size increased as quality metrics improved.

Conclusions: These results demonstrate a modest but reliable reduction in mPFC glutamate in SZ and suggest a similar reduction in DLPFC glutamate, with effect sizes scaling directly with metrics sensitive to the quality of glutamate measurements. Theoretical and methodological implications of these findings are discussed.

Keywords: Magnetic Resonance Spectroscopy, Schizophrenia, Meta-Analysis

Disclosure: Nothing to disclose.

T144. Neurite Orientation Dispersion and Density Imaging (NODDI) and Duration of Untreated Psychosis in Antipsychotic Medication-Naïve First Episode Psychosis Patients

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Background: Diffusion tensor imaging suggests that white matter alterations are already evident in first episode psychosis patients (FEP) and may become more prominent as the duration of untreated psychosis (DUP) increases. But because the tensor model lacks specificity, it remains unclear how to interpret findings on a biological level. Here, we used a biophysical diffusion model, Neurite Orientation Dispersion and Density Imaging (NODDI), to map microarchitecture in FEP, and to investigate associations between DUP and microarchitectural integrity.

Methods: We scanned 78 antipsychotic medication-naïve FEP and 64 healthy controls using a connectome-style multi-shell diffusion weighted sequence and used the NODDI toolbox to compute neurite density (ND), orientation dispersion index (ODI) and extracellular free water (FW) maps. AFNI's 3dttest++ was used to compare diffusion maps between groups and to perform regression analyses with DUP.

Results: We found that ND was decreased in commissural and association fibers but increased in projection fibers in FEP. ODI was largely increased regardless of fiber type, and FW showed a mix of increase in decrease across fiber tracts. We also demonstrated associations between DUP and microarchitecture for all NODDI indices.

Conclusions: We demonstrated that complex microarchitecture abnormalities are already evident in antipsychotic-naïve FEP. ND alterations are differentially expressed depending on fiber type, while decreased fiber complexity appears to be a uniform marker of white matter deficit in the illness. Importantly, we identified an empirical link between longer DUP and greater white matter pathology across NODDI indices, underscoring the critical importance of early intervention in this devastating illness.

Keywords: First Episode Psychosis, Diffusion Weighted Imaging, Duration of Untreated Psychosis

Disclosure: Neurocrine Biosciences, Inc.: Advisory Board (Self); American Board of Psychiatry and Neurology: Consultant (Self)

T145. N-Acetylcysteine Increases Glutathione in Schizophrenia Medial Prefrontal Cortex: A Preliminary Study

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Background: Neuroinflammation and oxidative stress are implicated in the etiology of schizophrenia in that excess

neuroinflammation may lead to neuronal trauma via oxidative stress. The antioxidant defense system (AODS) is designed to counterbalance the negative effects of oxidative stress. In schizophrenia, key components of the AODS are reduced, including levels of glutathione. Previous magnetic resonance spectroscopy (MRS) studies have shown decreased glutathione in the medial prefrontal cortex in patients. This reduction may have the downstream effect of reducing the efficiency of NMDA-type glutamate receptors on inhibitory neurons in schizophrenia, contributing to excess glutamate signaling in the dorsolateral prefrontal cortex.

N-acetylcysteine (NAC), an amino acid available as an oral supplement, is able to affect both glutathione and glutamate. As a precursor to glutathione, NAC is hypothesized to correct deficits in glutathione by increasing its concentration at synapses. Additionally, within the glutamate system, it is thought that NAC acts on inhibitory neurons to restore inhibitory tone on glutamatergic neurons in the prefrontal cortex. This raises the possibility that NAC may be able to counteract aberrations in glutathione and glutamate in prefrontal cortex in schizophrenia. Indeed, supplementation via oral administration of N-acetylcysteine has been linked to reduced cognitive impairment and negative symptoms.

To investigate this possibility, we conducted a randomized, double-blind, placebo-controlled preliminary study to examine the effects of N-acetylcysteine administration on levels of glutathione and glutamate in medial and dorsolateral prefrontal cortex of patients with chronic schizophrenia. We also performed measures of cognition, symptoms, and level of functioning.

Methods: Patients with schizophrenia were randomized to either N-acetylcysteine (NAC, $N = 15$) 2400 mg by mouth daily (1200 mg twice daily) or placebo ($N = 15$) in an eight-week treatment study (NCT02505477). All subjects met DSM-5 criteria for schizophrenia or schizoaffective disorder. Exclusion criteria included moderate or severe substance use disorder, antipsychotic medication dosage change greater than 50%, or psychiatric hospitalization, within the prior 3 months. Glutathione was measured using a specially adapted MRS sequence based on MEGA-PRESS, and glutamate was measured with PRESS. Voxels were placed based on individual subjects' anatomical landmarks in the medial prefrontal cortex (MPFC) and dorsolateral prefrontal cortex (DLPFC). Psychotic symptoms were measured with the 7-item positive symptom sub-scale of the Positive and Negative Symptom Scale (PANSS-P), negative symptoms with the Clinical Assessment Interview for Negative Symptoms (CAINS), cognition with the MATRICS Consensus Cognitive Battery (MCCB), and functional outcomes with the Role Functioning Scale (RFS). Mixed model linear regression was used to examine interactions between treatment group and time for the above measures.

Results: The study sample was 80% male, had a mean age of 54.3 years (SD 8.9), and had a mean chlorpromazine equivalent antipsychotic medication dosage of 652 mg (SD 404 mg). Mean duration of illness was 32 years (SD 11.5). At baseline, mean of the seven-item positive symptom sub-scale of the PANSS was 13.8 (SD 7.0); mean CAINS total score was 18.2 (SD 8.0).

We found a significant treatment effect for increased glutathione levels in MPFC ($F(1,30.2) = 4.86$, $p = 0.035$) and a trend-level treatment effect for reduced glutamate levels in DLPFC ($F(1,30) = 4.04$, $p = 0.054$). However, it is possible that these two effects could be explained by regression to the mean, although such a potential confound was not observed in other measures. No interaction or main effects of cognition, symptoms, or function were identified.

Conclusions: In a small, randomized, double-blind, placebo-controlled study, NAC treatment (2400mg daily) was associated with increased glutathione in the MPFC of patients with schizophrenia measured with MRS. NAC treatment was also associated with a trend level decrease in glutamate, in the DLPFC. Both findings could be explained by regression to the mean. These results offer conditional support for further research into the utility of NAC for improvement of oxidative states and glutamate signaling in schizophrenia.

Keywords: Neuroinflammation, N-acetylcysteine, Schizophrenia (SCZ), Magnetic Resonance Spectroscopy, Glutamate

Disclosure: Nothing to disclose.

T146. Systematic Review and Meta-Analysis of NMDA Receptor Autoantibodies in Psychotic Disorders

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Background: The relationship between anti-N-methyl D-aspartate (NMDA) receptor (NMDAR) autoantibodies and schizophrenia is inadequately understood, as studies examining this association have yielded inconsistent findings. IgG antibodies to the GluN1 subunit of NMDAR cause anti-NMDAR encephalitis, which can rarely present with isolated psychiatric symptoms. If a subset of individuals with schizophrenia have these autoantibodies, they may represent undiagnosed cases of anti-NMDAR encephalitis or a phenotype of schizophrenia that could be treatable with immunomodulation. We endeavored to synthesize research on this relationship through a systematic review and meta-analysis of studies examining the prevalence of NMDAR autoantibodies in psychotic disorders.

Methods: A structured search of PubMed, PsycInfo, and Web of Science was conducted in order to identify cross-sectional and longitudinal studies measuring circulating IgG antibodies to the GluN1 subunit of the NMDA receptor in adults with non-affective primary psychotic disorders. We also examined seroprevalence of IgA and IgM, which have unknown relevance for psychosis. Study population characteristics and assay type were noted as these factors contribute to substantial inter-study variance.

Results: We screened 1074 references and identified 68 papers for full review. Following full review, 28 papers met eligibility criteria. Very few studies reported actual NMDAR antibody titers, so we conducted a meta-analysis of the proportion of seropositivity across populations. IgG antibody seroprevalence in psychosis ranged from 0% to 9% in these studies. In the pooled analysis, positive antibody titers were low regardless of population. Individuals with first-episode psychosis had a non-significantly higher proportion of positive IgG subjects (2%; 95% CI 0–3%) than controls (1%; 95% CI 0–3%). IgG seropositivity was the same (1%) for all psychosis (95% CI 0–2%), non-first-episode psychosis (95% CI 0–1%), and controls. Controls had a non-significantly higher proportion of IgA (6%; 95% CI 2–11%) and IgM seropositivity (6%; 95% CI 2–11%) compared with individuals with psychotic disorders (IgA 5%; 95% CI 3-6% and IgM 4%; 95% CI 3-5%).

Conclusions: NMDAR antibody seroprevalence appears to be low in individuals with psychotic disorders. Nevertheless, assay type (particularly the use of fixation agents) has a pronounced impact on study findings. Most studies used assays that were specific for the diagnosis of anti-NMDAR encephalitis. Recent experimental models indicate that any IgG antibody to the GluN1 subunit could lead to NMDA dysfunction, suggesting that assays specific for antibodies associated with anti-NMDAR encephalitis may miss other NMDAR antibodies that could contribute to psychosis without causing encephalitis. Future research may benefit from casting a wider net by using assays that assess the full spectrum of GluN1 antibodies and subsequently examining the role of blood-brain barrier dysfunction in carriers of these antibodies.

Keywords: Psychosis, Autoantibody, NMDA Receptors, Schizophrenia, Immune Biomarkers

Disclosure: Nothing to disclose.

T147. Increased Density of Excitatory Synapses in the Substantia Nigra in Schizophrenia: A Postmortem Ultrastructural Study

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Background: Schizophrenia (SZ) is one of the most debilitating mental disorders with a prevalence of approximately 1%. The preponderance of evidence indicates that dopamine abnormalities are play a role in the illness are pathway specific and underlie different symptoms. Elevated striatal dopamine via the nigrostriatal pathway is associated with psychosis and has been implicated in SZ pathology since the development of antipsychotic drugs APDs and the discovery that the majority of neuroleptics block striatal dopaminergic D2 receptors. The substantia nigra (SN) houses one of the largest clusters of dopaminergic cells in the brain; however, few postmortem studies have examined the SN and ventral tegmental area (VTA) in SZ. Imaging studies have shown evidence for hyperactivity of the SN/VTA in SZs including excessive glutamate release, increased dopaminergic neuronal activity, and functional dysconnectivity correlated with excess dopamine release in the striatum. We hypothesized that increased excitatory neurotransmission and/or decreased inhibitory neurotransmission in the SN could underlie these imaging findings. To test this hypothesis, we performed a quantitative ultrastructural study of the SN/VTA in SZ subjects and matched controls. Synaptic morphology is highly linked to the type of neurotransmission, thus providing information about excitatory or inhibitory synapses in the absence of immunolabeling. Synapses with thick postsynaptic densities are called asymmetric (or Type I) and correspond to excitatory neurotransmission, while synapses with thin postsynaptic densities are called symmetric (or Type II) and correspond to inhibitory neurotransmission.

Methods: We examined postmortem SN from 11 schizophrenia patients (SZs), and 8 normal controls (NCs). The gender composition of the groups was mainly male. The racial composition of the groups was a combination of Caucasian and African American. The mean age per group was 43.3 ± 14.3 years and 47.6 ± 11.3 years for NCs and SZ, respectively. The mean postmortem interval was 5.7 ± 1.1 hours and 6.1 ± 2.3 hours for NCs and SZs, respectively. The mean volume analyzed per case was 2443.5 ± 838.0 μm3 and 1269.4 ± 521.9 μm3 in NCs and SZs, respectively. Synapses were counted based using stereological techniques. Synapses were classified by the thickness of the postsynaptic density, and the presence of a presynaptic density. Statistical outliers were identified and removed, the data was tested for normality, followed by parametric or nonparametric tests as indicated.

Results: Synapse morphology was much more diverse than the typical types of synapses defined by a thick or thin postsynaptic density (PSD). Most (65%) of the synapses in both groups had a presynaptic density, which has not been identified in previous literature. In both groups, the PSD of some synapses were neither thin nor thick; thus, the excitatory or inhibitory nature of these synapses is unknown. NCs had a mean combined (all morphologies) synaptic density of 0.040 ± 0.007 axon terminals per μm3, while SZs had a mean density of 0.067 ± 0.026 axon terminals per μm3 ($p < 0.008$). When dividing the synapses by the presence or absence of a presynaptic density, SZ subjects had significantly more synapses of both types than NCs: with a presynaptic density 0.032 ± 0.008 vs 0.022 ± 0.005, $p < 0.007$; without a presynaptic density 0.025 ± 0.014 vs 0.011 ± 0.005, $p < 0.028$. SZ subjects tended to have higher densities of each category of synapse divided by symmetry, but these trends did not reach statistical significance. When sorting by symmetry of synapse and presence or absence of a presynaptic density, SZ had a higher density of asymmetric (excitatory) synapses without presynaptic density than did NCs (0.012 ± 0.011 vs 0.003 ± 0.001, $p < 0.024$).

Conclusions: The human SN/VTA has a much more complicated synaptic architecture than in other brain areas, including a sizable proportion of synapses with PSDs of intermediate thickness and a large proportion of synapses with presynaptic densities. These unusual morphologies have unclear functional significance. In SZ, the higher density of asymmetric synapses suggests abnormally high excitation. Previous studies support this data showing that vGLUT2 protein, a marker of subcortical glutamate neurons, is increased in the SN/VTA in SN. Taken together, subcortical glutamatergic afferents provide increased excitation to neurons in the SN/VTA in SZ, which may play a role in the hyperactivity of dopamine neurons in the illness.

Keywords: Dopamine, Glutamate, Electron Microscopy

Disclosure: Nothing to disclose.

T148. Efficacy of Lumateperone (ITI-007) in Depression Symptoms Associated With Schizophrenia

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Background: In patients with schizophrenia, depression symptoms are often prevalent, even in stable patients following antipsychotic treatment. Depression associated with schizophrenia is linked to poorer patient outcomes, including increased risk of relapse and suicidality, worse functioning, and decreased quality of life. Lumateperone (lumateperone tosylate, ITI-007) is a mechanistically novel agent for the treatment of schizophrenia that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission. This mechanism of action may confer beneficial effects in treating depression symptoms associated with schizophrenia.

The efficacy, safety, and tolerability of lumateperone in schizophrenia was established in randomized, placebo-controlled studies. An open-label study (Study 303) in stable schizophrenia patients switched from prior antipsychotic (PA) treatment to 1 year of lumateperone 42 mg further supported the long-term effectiveness and safety of lumateperone.

This post hoc analysis of Study 303 evaluated the effects of lumateperone 42 mg across the range of depression symptoms in stable patients with schizophrenia.

Methods: Depression symptoms in Study 303 were assessed using the Calgary Depression Scale for Schizophrenia (CDSS). This scale comprises 9 items that are scored 0 (absent) to 3 (severe). Analyses were conducted in patients with moderate-to-severe depression symptoms (CDSS ≥ 6) at baseline. Mean change from baseline was analyzed with a paired *t*-test. A responder analysis (≥50% improvement from baseline) was also conducted.

Results: The overall population comprised 602 stable schizophrenia patients, of these, 80 patients had moderate-to-severe depression symptoms (CDSS score ≥ 6). Mean CDSS score in these patients was 7.6 (range 6–16). At the end of treatment (EOT) mean change from baseline was −4.8 ($P < 0.0001$); mean CDSS score was 2.4. In stable patients with CDSS score ≥6 at baseline, 50% responded by EOT. Improvements were seen in patients with and without concomitant antidepressant treatment.

Depression (Item 1) and Early Awakening (Item 7) were the most prominent symptoms at baseline (mean scores 1.5 and 1.1, respectively); Suicide (Item 8) was the least severe (0.1). At Day 75 (earliest on-treatment assessment), all CDSS items showed significant improvement ($P < 0.05$ to $P < 0.0001$) from baseline. The magnitude of improvement for all items increased from Day 75 to EOT (Day 368). The largest improvement was for Item 2 (Hopelessness; change from baseline = −0.8); 5 CDSS items

showed marked improvements (−0.6) including Item 1, Item 3 (Self Depreciation), Item 5 (Pathological Guilt), Item 6 (Morning Depression), and Item 7.

Conclusions: In stable schizophrenia patients with moderate-to-severe depression, lumateperone 42 mg significantly improved a broad range of depression symptoms. Clinically meaningful improvement of depression symptoms was achieved in 50% of patients. These results support the benefits of lumateperone 42 mg in treating depression symptoms associated with schizophrenia.

Keywords: Schizophrenia (SCZ), Antipsychotic, Depressive Symptoms

Disclosure: Intra-Cellular Therapies, Inc.: Employee, Stock / Equity (Self)

T149. SEP-363856, a Novel TAAR1 Agonist, Lacks Abuse Liability in Preclinical Models and Attenuates Cocaine Cue-Induced Relapse in Rats

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Background: SEP-363856 is a novel psychotropic agent with a unique non D2, non 5-HT2A mechanism of action which has shown broad efficacy across multiple animal models of psychosis. Sunovion discovered SEP-363856 in collaboration with PsychoGenics based in part on a mechanism-independent approach using the in vivo phenotypic Smartcube® platform and associated artificial intelligence algorithms. The molecular targets responsible for the antipsychotic efficacy of SEP-363856 are not fully elucidated but include agonist activity at trace amine associated receptor 1 (TAAR1) and 5-HT1A receptors. Based on its unique mechanism of action and preclinical profile in animal models, SEP-363856 appears to represent a promising candidate for the treatment of schizophrenia and potentially other neuropsychiatric disorders. Given its CNS activity and the novel mechanism of this new chemical entity, a series of preclinical studies were undertaken with SEP-363856 to evaluate potential risk for abuse.

Methods: Abuse-related animal behavioral studies (self-administration and drug discrimination) were conducted in rats to evaluate whether SEP-363856 produces behavioral changes suggestive of human abuse potential. In addition, studies were undertaken to probe the potential for SEP-363856 to block reinstatement of cocaine-seeking behavior in rats.

Results: SEP-363856 was not self-administered by rats trained to self-administer amphetamine, cocaine, or heroin. Over a behaviorally-active dose range, the subjective qualities of SEP-363856 were distinct from those produced by amphetamine in a drug discrimination procedure. SEP-363856, and buspirone, a non-scheduled anxiolytic with 5-HT1A partial agonist activity, partially generalized to the interoceptive cue elicited by 3, 4-methylenedioxymethamphetamine (MDMA). SEP-363856 demonstrated a trend to reduce reinstatement responding produced by cocaine primes and dose-dependently and significantly reduced cue-reinstated responding.

Conclusions: Based on the established predictive validity of the self-administration and drug discrimination behavioral paradigms in rats, these results suggest that SEP-363856 is not likely to pose a risk for recreational abuse in humans. Further, these results suggest the potential therapeutic utility of SEP-363856 in the treatment of substance use disorders that warrants further investigation given the purported role of TAAR1 in addiction.

Keywords: Abuse Liability, TAAR1, Cocaine Self-Administration

Disclosure: Sunovion Pharmaceuticals Inc.: Employee (Self)

T150. Molecular Mechanism of the Selectivity of the Antipsychotic Xanomeline at Muscarinic Receptors

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Background: Xanomeline is a potent agonist for the muscarinic acetylcholine receptor (mAChR) family. Karuna Therapeutics has successfully completed Phase 2 studies in a placebo-controlled schizophrenia trial with a xanomeline-trospium (KarXT) combination therapy and has initiated a Phase 1b trial in patients with dementia-related psychosis. Despite promising clinical results, both the structural basis of xanomeline binding to muscarinic receptors and its unusual selectivity among mAChR subtypes are poorly understood. The five mAChR subtypes differ substantially in biological function and tissue distribution but have conserved sequences and structure around the orthosteric ligand (acetylcholine) binding site. Thus, developing selective ligands, especially agonists, is a principal goal and challenge in this field. Research over the past 20 years has suggested that xanomeline more strongly activates M1 and M4 receptors, despite binding to the well-conserved orthosteric site. Without a molecular view of the drug-receptor interactions, it has been difficult to explain these desirable but mysterious properties and relate them to xanomeline's chemical structure. A molecular understanding would enable the rational design of new muscarinic agonists with tailored signaling properties across the family of mAChRs.

Methods: To systematically assess xanomeline's functional selectivity across all 5 mAChRs, we measured the level of ERK 1/2 phosphorylation in Chinese Hamster Ovary cells stably expressing each mAChR subtype. We then quantified the intrinsic efficacy of xanomeline and 7 designed analogs, correcting for receptor expression level differences between cell lines. To investigate molecular interactions with the receptor, we chose to focus on a comparison of the closely related M2 and M4 receptors. We first docked xanomeline to the orthosteric site of active M2 and M4 structures. We then conducted extensive molecular dynamics simulations of these systems embedded in a hydrated lipid bilayer with all atoms represented explicitly.

Results: In the pERK1/2 assay, xanomeline's intrinsic efficacy at M4 was significantly greater compared to the others receptor subtypes ($p < 0.01$, $N = 3$). Intrinsic efficacy at M4 was nearly doubled that of M2, with a 10-fold difference in potency. In contrast to previous reports, xanomeline did not activate M1 pERK significantly more than M2/3/5.

Using molecular dynamics simulations of M2 and M4 receptors, we discovered that xanomeline's hydrophobic hexyl tail interacts with unique cavities extending toward the membrane or extracellular space. These cavities are not accessed by other common muscarinic agonists. Xanomeline's tail frequently extends between transmembrane domains 5 and 6 (TM5-6) to contact membrane lipids. However, the interaction with this gap was significantly different between M2 and M4 ($p = 0.03$, $N = 6$). At M2, the tail moved closer to a key asparagine residue on TM6, rotating this residue away from its active state. Differing sequences on extracellular loop 2 and the membrane-facing surface of TM6 could drive this differing xanomeline behavior at M2 and M4. Thus, the extension of the tail into these cavities enables xanomeline to contact more diverse residues beyond the highly conserved orthosteric site.

To validate this model, we synthesized a series of xanomeline analogs with tails ranging from 1 to 8 carbons. We then used the pERK 1/2 assay to measure the intrinsic efficacy of these analogs. As predicted, shortening the tail from 8 to 3 carbons successively

reduced the difference in xanomeline efficacy between M2 and M4.

Conclusions: In these studies, xanomeline behaves as a M4 muscarinic receptor agonist and is considerably less active at the M1, M2, M3 and M5 receptors. Our results not only provide basic information about xanomeline's binding mode and activity, but also begin to explain this ligand's in vitro and in vivo selectivity at the molecular level. We discovered that xanomeline's tail selectively interacts with novel gaps between transmembrane helices. By bridging the orthosteric site and more sequence-diverse allosteric sites, agonists can achieve a degree of functional selectivity observed in some, but not all, in vitro and in vivo assays. This data may help explain xanomeline's antipsychotic activity in patients with schizophrenia and Alzheimer's disease.

Keywords: Acetylcholine Esterase Inhibitors, Muscarinic Receptors, Dementia, Xanomeline, Schizophrenia

Disclosure: Nothing to disclose.

T151. In Vivo Characterization of the Opioid Receptor Binding Profiles of Samidorphan and Naltrexone in Rats: Comparisons at Clinically Relevant Concentrations

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Background: A combination of olanzapine and the opioid receptor antagonist samidorphan (OLZ/SAM) is under development for the treatment of schizophrenia and bipolar I disorder. Samidorphan is a new molecular entity structurally related to naltrexone, but with differentiated characteristics. OLZ/SAM is intended to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain. In vitro, samidorphan binds with high affinity to mu (MOR), kappa (KOR), and delta (DOR) opioid receptors and functions as a MOR antagonist with partial agonist activity at KOR and DOR. Samidorphan binds with higher affinity to MOR, KOR, and DOR than naltrexone and functions as a more potent opioid receptor antagonist. The current studies characterize and compare the in vivo binding profiles of samidorphan and naltrexone at clinically relevant concentrations.

Methods: Two cohorts of male Sprague-Dawley rats were injected with 0.03-3 mg/kg SC samidorphan or 0.01-1 mg/kg SC naltrexone. The first cohort of rats was sacrificed to measure plasma and brain uptake. In the second cohort, thirty minutes after receiving samidorphan or naltrexone, rats were IV injected with a triple tracer of NTX-D3, naltriben, and GR103545 to measure MOR, DOR, and KOR occupancy, respectively. Brains were dissected and receptor occupancy of MOR, DOR, and KOR was measured using LC-MS.

Results: At clinically relevant concentrations, samidorphan occupied MOR, DOR, and KOR whereas naltrexone occupied only MOR and KOR. Corrected for free brain concentration, samidorphan also has higher in vivo affinity for MORs, KORs and DORs than naltrexone.

Conclusions: Based on these data, samidorphan has a differentiated binding profile from naltrexone.

Keywords: Samidorphan, Naltrexone, Opioid Receptors

Disclosure: Alkermes, Inc.: Employee (Self)

T152. Associations of Objective Sleep Assessments With Cognitive and Physical Functioning: A Cross-Sectional Study of Actigraphy in Community-Dwelling Participants with Schizophrenia and Non-Psychiatric Comparison Participants

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Background: Sleep disturbances are present in 30-80% of people with schizophrenia (PWS) are common and have been linked with older age, more severe positive symptoms, worse depression, worse cognitive functioning, increased inflammation, and worse metabolic dysfunction. Few studies have examined objective sleep patterns in PWS to understand the relationships between sleep and multiple domains of health (mental, cognitive, physical).

We present cross-sectional data from ongoing longitudinal studies of PWS and non-psychiatric comparison subjects (NCs). Our hypotheses were: 1) PWS would have worse self-reported sleep quality, shorter sleep duration, decreased sleep efficiency, and greater variability in sleep duration and efficiency. 2) Worse sleep measures would be related to worse mental, cognitive, and physical functioning as well as metabolic and inflammatory biomarker levels. We explored the impact of duration of overnight awakenings, Bed-Time, and Wake-Time (as well as variability in those measures) on health.

Methods: The sample included 25 PWS (DSM-IV-TR criteria) and 38 NCs (mean age 51.0 years, SD 11.9, range 29 to 72 years). People with dementia were excluded.

Participants wore Actigraph Link devices (ActiGraph Inc., Pensacola, FL) for 4 to 12 days/nights, a wrist-worn tri-axial accelerometer that is valid and reliable in PWS. Sleep measures included total sleep time (TST), sleep efficiency, wake after sleep onset (WASO, total duration of overnight awakenings), bed-time, and wake-time. Standard deviations (SDs) of sleep measures were considered to look at the influence of intra-individual variability on outcomes. Self-reported sleep quality was assessed using the Pittsburgh Sleep Quality Index.

Psychopathology measures included Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS, respectively) and the Patient Health Questionnaire-9 (for depression). Antipsychotic daily dose (WHO definition) and duration of illness were also assessed. Cognitive measures included executive functioning (Delis-Kaplan Executive Function System) and global cognition (Telephone Interview for Cognitive Status - modified.) We examined physical well-being (36-item Medical Outcomes Survey – Short form), physical comorbidities (Cumulative Illness Rating Scale), and body mass index (BMI).

Blood-based biomarkers assessed inflammation (high-sensitivity C-reactive protein or hs-CRP) and metabolic function (Hemoglobin A1c).

Independent sample *t*-tests and Mann-Whitney U tests were used to assess differences between PWS and NCs. Spearman's correlations were performed to assess the relationships of sleep measures with demographic and clinical variables as well as biomarker levels. General linear models (GLMs, controlling for age, sex, diagnostic group, and SD of the sleep measure) were conducted to assess the impact of sleep measures on health.

Results: PWS and NCs were comparable on age, sex, and race. The PWS group had fewer years of education and smoked more than the NCs. PWS had worse psychopathology, lower cognitive functioning scores, worse physical health, higher BMI, and elevated Hemoglobin A1c levels.

PWS had similar mean TST, efficiency, Bed-times, and Wake-times compared with the NCs. PWS had lower mean WASO (Mann Whitney U = 280.5, $p = 0.006$, d = 0.75), and greater TST SD and bed-time than the NCs (Mann Whitney U = 681.0, $p = 0.004$, d = -.86; and Mann Whitney U = 693.0, $p = 0.002$, d = −0.83; respectively). PWS had worse self-reported sleep quality (t(52)= −2.93, $p = 0.005$, d = 0.80). Self-reported sleep quality was not correlated with any objective sleep measure.

Older age was associated with greater sleep efficiency SD ($r = 0.41$, $p = 0.04$). Women had longer mean TST (t(61) = 2.45, $p = 0.02$,d = 0.62), earlier mean Bed-Time (t(61)=-3.53, $p = 0.001$, d =

−0.89), and lower sleep efficiency SD (Mann Whitney U = 642.0, p = 0.05).

There was a trend association between greater mean TST and better overall cognitive functioning (B = 0.011, Se = 0.006, p = 0.06, ηp2 = 0.06). Sleep measures were not associated with depressive symptoms, and among the PWS, sleep measures were not associated with antipsychotic daily dose, duration of illness, or severity of positive and negative symptoms.

In the entire sample, greater mean TST and diagnostic group were associated with lower BMI (B = −0.02, SE = 0.009, p = 0.04, ηp2 = 0.13; B = −6.4, SE = 2.07, p = 0.004, ηp2 = 0.23; respectively). Higher variability of sleep efficiency and female sex were associated with higher number of physical comorbidities (B = 0.31, SE = 0.11, p = 0.006, ηp2 = 0.14; B = 2.1, SE = 0.86, p = 0.02, ηp2 = 0.10; respectively). Greater mean TST and diagnostic group were associated with lower Hemoglobin A1c levels (B = −0.004, SE = 0.002, p = 0.03, ηp2 = 0.15; B = −1.0, SE = 0.33, p = 0.004, ηp2 = 0.24; respectively). Sleep measures were not associated with hs-CRP levels.

Conclusions: Sleep disturbances associated with schizophrenia may mediate some of the downstream health consequences. PWS had similar mean objective sleep measures, but greater variability of TST and bed-time than NCs. Sleep disturbances were associated with worse cognitive and physical functioning. Mean TST and variability of sleep efficiency were associated with physical health outcomes (BMI, physical comorbidities, and Hemoglobin A1c levels). Sleep is a promising lifestyle target for improving cognitive and physical functioning among PWS. This study is ongoing and updated results will be presented at the meeting.

Keywords: Sleep, Psychosis, Cardiometabolic Risk

Disclosure: Nothing to disclose.

T153. Altered Transcranial Magnetic Stimulation Electroencephalographic Markers in Schizophrenia

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Background: Cortical inhibition is a neurophysiological process in which cortical gamma-aminobutyric acid (GABA) inhibitory interneurons modulate the activity of pyramidal neurons in the cerebral cortex. Multiple lines of evidence, including neurophysiological and neuropathological, report that individuals with schizophrenia have deficits in cortical inhibition. Combining transcranial magnetic stimulation (TMS) with electroencephalography is a reliable approach to measure inhibitory processes in the cortex. The overall waveform produced by TMS-EEG may index cortical reactivity as a whole and previous investigations have linked the N45 component peak and the N100 component peak with GABA-A and GABA-B inhibitory neurotransmission, respectively. The aim of this study was to stimulate the DLPFC with TMS and examine resultant differences in the TMS-EEG waveform peaks between patients with schizophrenia and healthy subjects. We hypothesized that individuals with schizophrenia will have smaller TMS-evoked potentials, specifically the amplitudes of the N100 and N45 components, those previously related to GABA-ergic inhibition.

Methods: We applied TMS over the left DLPFC and recorded EEG activity in 48 healthy subjects (mean age: 33.8 ± 5.3) and 46 patients with schizophrenia (mean age: 43.3 ± 6.4). Monophasic TMS pulses were administered using a 7-cm figure-of-8 coil, and two Magstim 200 stimulators connected via a Bistim module. Single pulse TMS was administered over the left DLPFC with 100 total pulses, which were delivered every 5s. Resultant waveforms were extracted and analyzed through custom MATLAB scripts. The TMS-evoked potential waveform was examined through Global Mean Field Amplitude (GMFA) analysis of waveform peaks in each the two groups. Normality of the distribution of each variable was assessed and a Mann Whitney U test was then performed for each variable of interest to assess differences between groups.

Results: Individuals in the schizophrenia group demonstrated smaller measures of cortical inhibition in the DLPFC. Specifically, smaller amplitudes of the N45 (U = 724.00, p = 0.004) and N100 peaks (U = 831.00, p = 0.039), although the overall AUC of the waveform did not differ between groups (U = 969.00, p = 0.307). Further analysis is underway to examine medication and symptom cluster effects.

Conclusions: These results demonstrate novel findings of deficits in both GABA-A and GABA-B associated measures of cortical inhibition as indexed by single pulse TMS-EEG. This reinforces previous evidence from different research modalities demonstrating overall GABAergic inhibitory deficits in schizophrenia, and specifically provides new support which confirms recent findings of aberrant GABA-Aergic inhibitory neurotransmission in schizophrenia.

Keywords: Schizophrenia (SCZ), TMS-EEG, Cortical Inhibition, GABA

Disclosure: Nothing to disclose.

T154. Hippocampal Volume in Early Psychosis: A Two-Year Longitudinal Study

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Background: A hippocampal volume deficit is one of the most widely replicated findings in schizophrenia. However, the evolution of this volume deficit in the critical period following illness onset is unclear. We followed patients in the first 2 years of a psychotic disorder to examine longitudinal changes in hippocampal structure. In our primary analysis, we tested the hypothesis that hippocampal volume decline in the first two years of illness is regionally specific, with the anterior cornu ammonis (CA) subfields most affected. In a secondary analysis, we examined the impact of illness trajectory on hippocampal volume change over two years. Approximately one-third of individuals diagnosed with schizophreniform disorder will not experience persistent illness leading to a diagnosis of schizophrenia. We predicted that hippocampal volume is reduced only in individuals who will ultimately be diagnosed with schizophrenia.

Methods: We analyzed longitudinal structural MRI data from 63 early psychosis patients and 63 healthy control subjects, collected over two years. Fifty-six early psychosis (89%) and 52 healthy control subjects (83%) completed the study. We measured subfield volumes in the anterior and posterior regions of the hippocampus using the longitudinal processing stream of Freesurfer 6. Data were analyzed by fitting linear mixed models of volume, with group, region, and subfield as fixed effects, and participant as a random effect.

Results: We found lower hippocampal volume in the early psychosis group in the anterior rather than the posterior region (Group X Region interaction: p = 0.02, d = 0.74). However, this deficit did not change over two years (Group X Region X Time interaction: p = 0.95). In our secondary analysis, we observed regionally specific hippocampal volume deficits that varied with diagnostic trajectory (Trajectory X Region X Subfield interaction: p = 0.04). Anterior CA volume was lower than healthy individuals in participants who met criteria for schizophrenia at baseline (p < 0.001, d = 0.83) and in participants who were diagnosed with

schizophrenia after two years ($p < 0.001$, d = 1.24). Participants who maintained a diagnosis of schizophreniform disorder over two years had anterior CA volume similar to healthy individuals ($p = 1.0$). These group differences did not change over time (Trajectory X Region X Subfield X Time interaction: $p = 1.0$).

Conclusions: In a longitudinal case-control design, we find that anterior hippocampal volume is lower in early psychosis and does not decline further over the next two years. Additionally, we find smaller anterior CA volume at baseline only in those individuals who will ultimately progress to schizophrenia, not in those whose psychosis remits. Our data are consistent with a neurodevelopmental model of schizophrenia and suggest that anterior CA integrity is an important marker of clinical progression in psychosis.

Keywords: Schizophrenia (SCZ), Hippocampus, Structural MRI, Illness Trajectory

Disclosure: Nothing to disclose.

T155. Three Non-overlapping Cortical Interneuron Subtypes Relate to Distinct EEG Biomarkers in Neuropsychiatry

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Background: Schizophrenia and other neuropsychiatric disorders involve fundamental dysfunctions in perceptual processing. Electroencephalographic (EEG) recordings during sensory "oddball" paradigms have been utilized in patient populations to measure "biomarkers" of such deficits, such as the classic "mismatch negativity" (MMN) and the P300 scalp potential. Unfortunately, the basic molecular, cell, and circuit-level pathology that are indexed by such surface-level biomarkers remain unclear, representing a significant knowledge gap for developing a rapid, non-invasive, low-cost clinical assay of a defined biological pathology.

Methods: Here we studied the activity of cortical microcircuits in awake male and female mice ($n = 20$) during a classic visual oddball paradigm, with rare "deviant" stimuli (oriented drifting square-wave gratings) interspersed among repetitive "standard" stimuli (10% deviants). With fast two-photon calcium imaging (GCaMP6s; 28-Hz) in transgenic mice we recorded the activity of neural populations (n = 20-200 cells at once) across neocortical layers 1-5a, focusing on genetically tagged excitatory neurons and GABA-ergic inhibitory interneurons from three non-overlapping categories: parvalbumin (PV+), somatostatin (SST+), and vasoactive intestinal peptide (VIP+) positive cells. Further, we measured local field potential oscillations in the same paradigm with multielectrode probes spanning all cortical laminae to understand how the dynamics of these cell types relate to distinct frequency bands present in the human EEG.

Results: Neural responses during the oddball paradigm exhibited two components: stimulus specific adaptation (SSA; suppressed responses to repetitive stimuli) and deviance detection (DD; increased responses to deviant/oddball stimuli, suggestive of "prediction error"). Excitatory neurons displayed SSA across all layers, but only displayed genuine deviance detection in supragranular layers. Interneuron subpopulations (PV+, SST+, VIP+) showed highly diverse dynamics during this paradigm, both within and between cell types and layers. Numerous effects were present, but included strong adaptation to repetition (SSA) in layer 2/3 SSTs while 2/3 VIPs showed inverse adaptation, consistent with the mutual inhibition demonstrated between these populations in anatomical studies. In contrast, layer 4 SSTs, which have been shown to disinhibit excitatory cells, displayed deviance detection. Interestingly, VIPs correlated directly with layer 2/3 gamma oscillations, while layer 4 SSTs correlated with layer 4 theta/alpha oscillations.

Conclusions: While the MMN and p300 EEG potentials have shown promise as clinical biomarkers, these results emphasize that distinct cell and circuit biology may relate more directly to more nuanced components of these measures, such as sensory adaptation, prediction error, and neural oscillations. Given that GABA-ergic interneurons are known to show abnormalities in postmortem brain samples from people with psychosis, this work may provide an important roadmap for the refinement of clinical biomarkers and the development of precision therapeutics targeting cells and circuits.

Keywords: Cortical GABA, Two-Photon Calcium Imaging, Predictive Coding

Disclosure: Nothing to disclose.

T156. Molecular and Circuit-Specific analysis of Locus Coeruleus-Prefrontal Networks During a Touchscreen Rodent Continuous Performance Test

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Background: Attentional deficits are a prominent symptom in schizophrenia (SCZ), attention deficit hyperactivity disorder (ADHD), and major depressive disorder (MDD). Patients with these disorders frequently exhibit impairments in the continuous performance test (CPT), which is designed to measure sustained attention. Individuals with these disorders show aberrant prefrontal cortex (PFC) activity during CPT performance, suggesting that PFC dysfunction underlies attention deficits in these patients. However, the mechanisms by which the PFC regulates sustained attention during the CPT remain unclear.

Methods: Behavioral testing and c-Fos immunohistochemistry were used to assess activation of inputs to the medial PFC (mPFC) during performance of a rodent analogue of the CPT (the rCPT) in mice ($n = 6$ per group). In vivo calcium imaging ($n = 4$ mice) was used to assess patterns of activity in mPFC neurons, as well as mPFC neurons with connections to the locus coeruleus (LC) during the rCPT. Imaging of norepinephrine activity in the mPFC with a biosensor (GRAB_NE) was used to examine norepinephrine signaling during rCPT performance ($n = 4$). In vivo electrophysiology was employed to detect how the mPFC and LC communicate during the rCPT ($n = 4$). For assessment of molecular function in subsets of mPFC neurons that receive contact from the LC, we used RNAscope ($n = 10$) and bulk RNA-sequencing (n = 5).

Results: We found that a larger proportion of LC neurons with projections to the mPFC co-expressed c-Fos following rCPT performance ($t(22) = 3.086$, $p = 0.005$) as compared to a yoked behavioral control group. We further found that the LC and mPFC synchronized their activity during the rCPT, as evidenced by an increase in mPFC-to-LC directionality in the theta frequency band ($p < 0.001$) when the animal made a behavioral response, and an increase in LC-to-mPFC directionality in the gamma frequency band when the animal oriented attention to the stimulus ($p < 0.001$). Imaging of neuronal activity in the mPFC revealed that mPFC neurons have heterogeneous response patterns during rCPT performance, with some neurons increasing their calcium activity during stimulus orientation and some neurons increasing their calcium activity during behavioral responses. To determine the molecular identities of mPFC neurons that connect with the LC, we used RNAscope to find that mPFC neurons receiving LC contact are primarily GABAergic, while mPFC neurons projecting

to the LC are primarily excitatory ($F(1,6) = 190.2$, $p < 0.0001$). We further found that synthetic depolarization of LC neurons with projections to the mPFC increased Fos expression in GABAergic neurons ($F(1,6) = 8.426$, $p = 0.027$) and neurons expressing Adra1a ($p < 0.05$). Using bulk RNA-sequencing, we further found that depolarization of LC inputs to the mPFC caused enrichment of a host of transcripts in mPFC tissue.

Conclusions: Interactions between the locus coeruleus and mPFC are a critical component of rCPT performance in rodents, with the LC driving the mPFC during stimulus orientation, and the mPFC driving the LC during behavioral responding. These results have implications for brain function in patients with neuropsychiatric disorders who have deficits in CPT performance. Furthermore, we uncover unique molecular markers of neuronal function in this circuit, providing insight into potential therapeutic targets for attentional regulation in disorders such as ADHD, major depressive disorder, and schizophrenia.

Keywords: Attention, Medial Prefrontal Cortex, Noradrenaline, Touchscreen, RNA-Sequencing

Disclosure: Nothing to disclose.

T157. Effect on Cognitive Performance of the Dual Orexin Receptor Antagonist Lemborexant Compared With Suvorexant and Zolpidem

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Background: Lemborexant (LEM) is a dual orexin receptor antagonist approved in the US and Japan at doses up to 10 mg for the treatment of insomnia in adults. Drug abuse potential of LEM was examined in a phase 1 clinical trial, which included assessments of drug liking and cognitive performance. Reported here are the results from the assessment of cognitive performance following LEM treatment compared with zolpidem (ZOL), suvorexant (SUV), and placebo (PBO).

Methods: This was a single-center, single-dose, randomized, double-blind, 6-way crossover study (NCT03158025; E2006-A001-103) with adult subjects that were healthy, nondependent, recreational sedative users aged 18-55 years. The objectives of this study were primarily to evaluate the relative abuse potential of LEM and, secondly, to evaluate the safety profile (including assessments of cognitive performance) and pharmacokinetic profile following single dose administration of LEM. All subjects who entered the treatment phase could discriminate/like both SUV and ZOL versus PBO during a qualification phase. During the treatment phase, cognitive performance was assessed for oral doses of LEM (10mg [LEM10]; 20mg [LEM20]; 30mg [LEM30]) vs PBO and vs 2 active comparators (ZOL immediate release 30mg and SUV 40mg). All medications were administered following an overnight fast, with a ≥14 day washout between treatments. The primary endpoint of this study was to assess the peak maximum effect of LEM vs PBO, SUV, and ZOL on "at this moment" drug liking (not reported here). Cognitive performance assessments included the Choice Reaction Time (CRT) and the Divided Attention Test (DAT), which were assessed pre-dose and at regular time points from 15 minutes to 24 hours following study drug administration. CRT provides a measure of psychomotor performance and includes: recognition reaction time (RRT; the time it takes for a subject to notice the light by lifting their finger from the button; higher scores indicate greater impairment), motor reaction time (MRT; time between subject lifting their finger from the button and pressing the response button; higher scores indicate greater impairment), and total response time (TRT; sum of RRT and MRT; higher scores indicate greater impairment). DAT is a manual tracking test with a simultaneous visual target detection component; assessments included the percent of target hits (lower scores indicate greater impairment) and the number of false alarms (higher scores indicate greater impairment).

Results: A total of 32 subjects received and completed all treatments. In the primary assessment of "at this moment" drug liking, all doses of LEM, SUV, and ZOL demonstrated abuse potential vs PBO, and all doses of LEM were similar to SUV and ZOL (reported separately). For RRT, mean maximum change from baseline (CFBmax) scores were statistically significantly greater vs PBO (82.4ms) for all LEM doses (LEM10, 164.8ms; LEM20, 172.8ms; LEM30, 181.8ms; all P<0.001), and for ZOL (164.2ms; P<0.001) and SUV (143.6; P=0004). For all doses, LEM was not statistically significantly different compared with ZOL or SUV. For MRT, mean CFBmax scores vs PBO (44.3ms) were statistically significantly greater for all LEM doses (LEM10, 86.6ms; LEM20, 102.9ms; LEM30, 97.9ms; all $P < 0.001$), and for ZOL (227.4ms; $P < 0.001$) and SUV (83.0ms; $P < 0.001$). All LEM doses showed statistically significantly lower mean CFBmax (smaller increase in MRT) scores compared with ZOL (all $P < 0.001$), but not compared with SUV. For TRT, mean CFBmax scores vs PBO (99.3ms) were statistically significantly greater for LEM (LEM10, 229.5ms; LEM20, 246.7ms; LEM30, 258.7ms; all $P < 0.001$), and for ZOL (359.4ms; $P < 0.001$) and SUV (197.7ms; $P < 0.001$). Mean CFBmax score for LEM30 was statistically significantly greater compared with SUV ($P = 0.025$). All LEM doses showed statistically significant lower mean CFBmax scores compared with ZOL (all $P < 0.001$).

For DAT target hits, the mean minimum CFB (CFBmin) scores vs PBO (−17.8%) were statistically significantly lower for all LEM doses (LEM10, −43.3%; LEM20, −43.8%; LEM30, −45.6%; all $P < 0.001$), and for ZOL (−62.1%; $P < 0.001$) and SUV (−36.7%; $P < 0.001$). All doses of LEM showed statistically significantly greater CFBmin (smaller decrease in percentage of target hits) scores compared with ZOL (all P<0.001). LEM20 and LEM30 showed a statistically significantly greater decrease in the percentage of target hits compared with SUV ($P = 0.028$ and $P = 0.003$, respectively). For number of DAT false alarms, mean CFBmax scores were lowest with LEM (LEM10, 5.8; LEM20, 4.5; LEM30, 7.4), followed by SUV (7.5), PBO (9.2), and ZOL (10.5). Only mean CFBmax for ZOL was statistically significantly different compared with PBO ($P = 0.009$). All doses of LEM were statistically significantly different than ZOL ($P = 0.002$, $P = 0.001$, $P = 0.025$, respectively), but not SUV.

Conclusions: While all active treatments generally increased reaction time vs PBO, results of the CRT suggest that all doses of LEM were associated with less delay in reaction times compared with ZOL but were generally similar to SUV. Additionally, divided attention capabilities were significantly better with all doses of LEM compared with ZOL. Together, these results suggest that ZOL has a greater negative effect on cognitive performance in this subject population of recreational sedative users than LEM and SUV, although all 3 drugs have been placed in schedule IV and have a similar potential for abuse.

Keywords: Lemborexant, Insomnia, Cognition, Abuse Potential

Disclosure: Eisai Inc.: Employee (Self)

T158. Sleep Disruption, and Other Behavioral Alterations, During Withdrawal Following Chronic THC Exposure in Mice

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Background: The diagnosis of cannabis withdrawal (DSM-V) has become less contentious at the clinical level given the growth of

human studies reporting withdrawal symptoms upon cessation of cannabis use. However, because reliable, objective measures of withdrawal from delta-9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, are generally difficult to observe in laboratory animal models, back-translational studies on the physiological mechanism of cannabis/THC withdrawal are lacking. Typically, in laboratory animal studies, withdrawal symptoms are precipitated by treatment with a cannabinoid type 1 receptor antagonist, which does not mimic the normal course of withdrawal in human cannabis users. A known consequence of chronic cannabis use in humans is altered sleep, and sleep disturbances are often cited as a primary withdrawal symptom upon cannabis cessation. Our laboratory has previously reported a role for endogenous cannabinoid signaling in sleep stability in mice, and we have recently aimed to determine if cannabis withdrawal-induced changes in sleep can be modeled in rodents.

Methods: We used electrocorticogram and electromyogram recordings from chronically implanted female and male mice combined with our fully automated sleep analysis system to score sleep before, during, and after chronic injection of either THC or vehicle control. We used a THC treatment regimen known to produce tolerance, consisting of ten i.p. injections of 10mg/kg THC over six days.

Results: Our findings indicate that polysomnographic measures in mice treated with THC indeed mimic clinical observations of altered sleep architecture in human cannabis users, including: 1) augmented total time spent in non-rapid eye movement (NREM) sleep after the first THC injection which returns to baseline levels after the last injection – i.e. tolerance to the sleep altering effects of the THC; and, 2) Destabilization of NREM and rebound of REM sleep during early abstinence (days 1–3) that progressively returns to control levels during later abstinence (days 4–6). To our knowledge, this is the first murine model of a directly translatable non-precipitated (spontaneous) cannabis withdrawal symptom. Our initial follow-up experiments indicate withdrawal-timepoint specific alterations in dopamine levels (as measured by ex-vivo fast-scan cyclic voltammetry) within the striatum, a brain region at the nexus of both drug addiction and sleep; and changes in behavioral indices associate with anhedonia and motivation during early, but not late timepoints of THC withdrawal. Lastly, we are beginning to uncover sex-differences in both sleep and behavioral measurements that highlight importance of including sex as a biological variable at both the preclinical and clinical level when studying effects of THC administration and withdrawal.

Conclusions: These data open the door for pre-clinical research efforts to determine the neurobiological bases of, and potentially treat, a primary withdrawal symptom of cannabis use disorder.

Keywords: Cannabis, Dopamine, Polysomnography, Anhedonia, Striatum

Disclosure: Nothing to disclose.

T159. Sleep Dynamics, Weight, and Appetite in a Prospective Cohort of Psychiatric Patients During COVID-19

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Background: Disrupted sleep is associated with an increased risk of all-cause mortality, weight dysregulation, adverse psychological symptoms and changes in eating behaviors, as well as altered leptin and inflammatory markers. Recent studies have suggested that the Coronavirus 2019 (COVID-19) pandemic has led to a shifted circadian rhythm with or without changes in sleep duration, but there is a limited understanding of how this has impacted the more vulnerable psychiatric patient populations. Furthermore, longitudinal studies on sleep dynamics during the acute pandemic period are lacking.

Methods: Participants were adult patients engaging in outpatient psychiatric treatment in an academic medical center in Madrid, Spain, with access to a smartphone and internet, who were being followed as part of an ongoing study using a smartphone-based ecological momentary assessment (EMA) program. On March 15, 2020, Spain issued a nation-wide quarantine as a public safety measure, and to assess the acute period surrounding the lockdown, we analyzed user-reported longitudinal sleep data gathered in the 6 weeks pre-lockdown (February 1 to March 14, 2020) and 6 weeks post-lockdown (March 15 to April 26, 2020) periods. Users were able to report their sleep and wake times in real-world, real-time, non-clinical settings through the smartphone-based EMA application. Past the acute phase of the pandemic (between May 12 to June 18, 2020), we gathered data on short-term psychological outcomes through remote clinical follow-ups, including the patients' retrospective recall regarding sleep habits pre- and post-lockdown, together with assessment of mood and anxiety symptoms using the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder 7-Item Scale (GAD-7) aimed at assessing recent emotional well-being past the acute phase of the pandemic. In the longitudinal arm, daily sleep durations and sleep timing were calculated for all participants, and the effects from time were assessed using linear mixed models with age, sex, and body mass index (BMI) as covariates. Further, systems-level changes in sleep patterns were assessed using the Mann-Kendall (MK) trend test with associated slope and change point calculations using Sen's and Pettitt's methods. For both longitudinal and retrospective recall data, sleep durations and bedtimes were compared across BMI groups using standard statistical tests for group differences. Linear regression modeling and Spearman's rank correlation methods were used to assess for association with psychological short-term outcome.

Results: Longitudinal data from $N = 58$ adult patients between the ages of 19 and 75 (mean ± SD = 45.8 ± 14.4), two-thirds female, with BMI ranging from 16 to 49 kg/m2 (underweight, UW = 7%; normal weight, NW = 40%; overweight, OW = 29%; and obese, OB = 24%) were available for the focused 12-week period surrounding the lockdown. Patients reporting insufficient sleep (<7 hours/night) had higher BMI (29.8 kg/m2 compared to 25.9 kg/m2, $p = 0.010$*) and delayed sleep timing (12:52 AM compared to 1:45 AM, $p = 0.009$**). Analysis of the real-time reported sleep data showed that patients have differential sleep patterns associated with BMI groups, with UW and OB patients reporting shorter sleep duration ($p = 0.004$**) and delayed bedtimes ($p = 0.047$*). Linear mixed models showed that sleep duration did not change over the course of the acute phase of the pandemic (F = 1.078, df = 84, $p = 0.302$) whereas the reported bedtimes were delayed significantly (F = 1.852, df = 84, $p < 0.0001$****). This pattern was mirrored in the system-wide time-series analysis in that there were no significant changes in sleep duration (MKtau = 0.008, Sen's Slope = 0.000, pSen = 0.912; pPettitt = 0.489) but the timing of sleep was significantly delayed (MKtau = 0.584, Sen's Slope = 84.102, pSen < 0.0001****; change point = March 18, 2020, pPettitt < 0.0001****). Analysis of the cross-sectional clinical data from $N = 212$ patients of similar age (19 to 77 years old), similar sex (two-thirds female) and BMI distribution (UW:NW:OW:OB = 4%:33%:36%:27%) inclusive of our longitudinal cohort also showed a shift towards delays in sleep-wake cycles through retrospective recall of pre- and post-lockdown periods after the acute pandemic period has ended. Shorter sleep duration during pre- and post-lockdown were highly correlated with overall depressive symptom scores, low mood, insomnia, suicidality and dysregulated appetite, and reported

sleep-timing in individuals with abnormal BMI acutely post-lockdown was significantly associated with dysregulated appetite ($p = 0.039$ *).

Conclusions: Psychiatric patients reported delayed sleep timing and similar sleep duration during the lockdown measures of the COVID-19 pandemic in Spain, and patients of abnormal BMI have disproportionately worse sleep patterns and psychological symptoms including appetite in the short-term following the longitudinal study. Further studies are needed to address if this affects other parameters of metabolic health and could lead to novel therapeutic strategies to address patients who may be at higher risk of psychiatric decompensation.

Keywords: Sleep, Metabolism, Circadian Rhythm, COVID-19, Ecological Momentary Assessment

Disclosure: Nothing to disclose.

T160. Kynurenic Acid Synthesis Inhibitor PF-04859989 Prevents Acute Kynurenine-Induced Sleep Disturbances in Rats

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Background: Individuals who suffer from neurocognitive disorders, such as age-related dementias, schizophrenia, or bipolar disorder, are often also battling sleep disturbances and comorbid parasomnias. Kynurenic acid (KYNA) is a tryptophan metabolite implicated in the pathophysiology of these illnesses. Modest increases in KYNA, which acts as an antagonist at N-methyl-D-aspartate (NMDA) and α7 nicotinic acetylcholine (α7nACh) receptors, and an agonist at the aryl hydrocarbon (AhR) receptors, result in cognitive impairments and alterations in sleep-wake behavior (Pocivavsek et al. Sleep 2017). We presently sought to determine if pharmacological inhibition of the KYNA synthesizing enzyme, kynurenine aminotransferase II (KAT II), may serve as a potential avenue to overcome sleep disturbances.

Methods: We explored the novel hypothesis that elevated KYNA adversely impacts sleep quality in adult cohorts of both male and female Wistar rats. Animals ($N = 9 – 11$ per sex within animal treatment design) were implanted with telemetric devices to acquire polysomnographic recordings that combine electroencephalogram (EEG) and electromyogram (EMG) and challenged with kynurenine, the direct precursor to KYNA. At the beginning of the light phase, rats received injections of either i) vehicle, ii) kynurenine (100mg/kg; i.p.), iii) the systemically active KAT II inhibitor, PF-04859989 (30 mg/kg; s.c), or iv) PF-04859989 and kynurenine in combination. Analysis of vigilance state-related parameters categorized as wake, rapid eye movement (REM) and non-REM (NREM) were assessed for 24 h after treatment.

Results: Kynurenine challenge significantly reduced REM duration by 15% compared to vehicle treatment (*$P < 0.05$) during the 12 h of the light phase. Animals treated with PF-04859989 thirty minutes prior to acute kynurenine challenge elicited unchanged REM sleep duration compared to vehicle treatment or PF-04859989 treatment alone ($P = 0.89$) during light phase analysis alone. Interestingly, PF-04859989 increased NREM duration (*$P < 0.05$) and decreased wake duration (*$P < 0.05$) across 24 hours in both vehicle and kynurenine-treated trials, suggesting that the KAT II inhibitor may have slight sedative properties. Furthermore, PF-04859989 enhanced NREM delta power in kynurenine-treated animals during the subsequent dark phase (*$P < 0.05$).

Conclusions: Taken together, REM was restored when PF-04859989 was administered prior to kynurenine challenge, suggesting that KAT II inhibition was sufficient to prevent the kynurenine-induced reduction in REM. Changes in NREM and wakefulness parameters elicited by the KAT II inhibitor may be indicative of mild somnolence induced by KAT II inhibition. The present and future complementary experiments provide mechanistic value to understanding the role of KYNA in modulating sleep behavior and demonstrate that KAT II inhibition may serve as a potential therapeutic avenue for improving sleep disturbances associated with neurocognitive disorders.

Keywords: Kynurenic Acid, REM Sleep, Schizophrenia (SCZ), Tryptophan Catabolites (TRYCAT), Kynurenine Pathway

Disclosure: Nothing to disclose.

T161. Role of Prefrontocortical Sigma-1 Receptors in the Post-Dependent Phenotype of Alcohol Addiction

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Background: Alcohol use disorder (AUD) is a highly prevalent chronically relapsing disorder characterized by compulsion to seek and take alcohol. AUD patients display loss of inhibitory control and cognitive deficits. These impairments are thought to be a result of chronic alcohol-induced neuroadaptations in fronto-cortical regions of the brain, including the anterior cingulate cortex (ACC), brain area key for the "top-down" inhibitory control over behavior, suggesting that hyperactivity of the ACC may play a key role in the development of alcohol addiction. Importantly, the ACC is also a hub for neuropathic pain and, therefore, a potential key site for alcohol-induced hyperalgesia. One promising therapeutic target for AUD has been proposed to be the Sigma-1 receptor (Sig-1R); blockade of this receptor has been shown to reduce excessive alcohol drinking and to alleviate neuropathic pain in rodent models. The aim of this study was, therefore, to examine the role of Sig-1R in the post-dependent phenotype resulting from the exposure of rats to chronic intermittent ethanol (CIE) vapor.

Methods: Subjects: Male Wistar Rats (250-275g upon arrival)

Chronic Intermittent Ethanol Exposure: Rats were subjected to repeated cycles of 14h on/10h inhalation of 95% ethanol vapor. Drip rate into the chamber was titrated to induce blood alcohol levels (BALs) of 150-200mg/dl, levels commonly seen in patients with AUD. BALs were confirmed weekly by taking 0.05ml of tail blood and testing it with an oxygen rate alcohol analyzer (Analox). Control rats were simply subjected to 24h air.

Immunofluorescence:

issue was sliced into 30μm thick sections using a cryostat and stored in cryoprotectant until use. Primary antibodies used rabbit anti-GluN2b (Alomone AGC 003; 1:700), mouse anti-Sig-1R (Santa Cruz sc137075; 1:250) and rabbit anti-GFP (Abcam ab6556 1:1000). Secondaries used were donkey anti-rabbit 488 (Invitrogen A21206; 1:400), donkey anti-mouse 555 (Invitrogen A31570; 1:400), goat anti-rabbit 488 (Invitrogen A32731; 1:400) and goat anti-mouse 555 (Invitrogen A32727; 1:400). Immunofluorescence studies used 4-6 animals/group.

Site Specific AAV Knockdown: Rats were stereotaxically infused (0.5 μl/side, 0.1 μl/min) with Sig-1R Adeno-Associated Virus (AAV) from the NIDA Optogenetics and Transgenic Technology Core to knockdown Sig-1R.

Testing for Mechanical and Thermal Sensitivity: Rats were tested for mechanical sensitivity using Von Frey filaments of increasing

force, according to the modified SUDO method. Rats were tested for thermal sensitivity using the Plantar Analgesia Meter (IITC). Using a beam of infrared light as the heat source, the stimulus was applied to each paw and latency to withdraw paw was recorded. These studies used 7-8 animals/group.

Testing for Impulsive Action via Differential Rates of Low Responding (DRL): Rats are trained to withhold lever pressing for a set amount of time (initially 5 sec (DRL5), then to 10 sec (DRL10) and eventually 15 sec (DRL15), in order to gain 0.1 ml of supersaccharin solution (1.5% glucose/0.4% saccharin). If the rat prematurely presses the lever (i.e. an incorrect response), no reward is given and the timer resets. Efficiency, a measure of impulsive action, is: rewarded responses / total (rewarded + incorrect) responses. These studies used 7–8 animals/group.

Statistical Analysis: Data examining the effect of CIE on pain states was assessed using an unpaired Student's t test; the effect of CIE on impulsive action was assessed using a 2-way mixed design ANOVA (CIE between-subjects factor, Withdrawal Time within-subject factor). Immunofluorescence data was analyzed with a factorial ANOVA (Withdrawal Time between-subjects factor) or an unpaired Student's unpaired t test (knockdown validation). Additionally, when ANOVAs proved significant, Newman Keul's was used for post-hoc comparisons.

Results: First, we found that CIE increased Sig-1R levels in the ACC during both acute (8–10 hours) and more protracted (3–4 days) withdrawal [$F(2,10) = 5.07$, $p < 0.05$]. To study the functional relevance of this change, we then used an adeno-associated virus to knock down Sig-1R in the ACC, and found that it reversed CIE-induced hyperalgesia [CIE x Virus: $F(1,27) = 8.83$, $p < 0.01$; CIE: $F(1,27) = 5.86$, $p < 0.05$; Virus: $F(1,27) = 2.90$, n.s.)] . On the other hand, Sig-1R knockdown in the ACC had no effect on either CIE-induced allodynia [CIE x Virus: $F(1,27) = 4.58$, $p < 0.05$; CIE: $F(1,27) = 2.87$, n.s.; Virus: $F(1,27) = 0.43$ n.s.] or increased impulsive action [CIE x virus x day: $F(6, 162) = 1.06$, n.s.; CIE x virus: $F(1,27) = 0.03$, n.s.; CIE x day: $F(6,162) = 2.88$, $p < 0.05$; CIE: $F(1,27) = 4.35$, $p < 0.05$); Virus: $F(1,27) = 0.65$, n.s.; Day: $F(6,162) = 2.96$, $p < 0.01$].

Conclusions: These data give important insights into the role of ACC and Sig-1R in alcohol addiction and associated pain states, and may lead to the development of novel pharmacological treatments for AUD.

Keywords: Alcohol, Pain, sigma-1 receptor

Disclosure: Nothing to disclose.

T162. HDAC5 in the Medial Prefrontal Cortex Regulates Drug Self-Administration and Seeking

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Background: Substance use disorder results in epigenetic alterations in brain regions critical to motivated behavior. Preclinical models of substance abuse have established that epigenetic changes underlie aspects of drug-taking and relapse to drug-seeking behaviors. These drug-induced changes in gene expression have been shown to promote drug seeking or to develop as a compensatory mechanism to oppose drug-mediated neuroadaptations. The neurocircuit originating in the prelimbic (PrL) subdivision of the medial prefrontal cortex (mPFC) and projecting to the nucleus accumbens (NAc) is heavily implicated in drug-seeking behavior. Recent work in our lab has functionally implicated the epigenetic enzyme, histone deacetylase 5 (HDAC5), in drug seeking behaviors. HDAC5 is a class IIa HDAC that is shuttled in and out of the cell nucleus in an activity-dependent manner, and delayed nuclear accumulation of HDAC5 after cocaine exposure serves as a 'brake'-like mechanism to limit drug-mediated changes in transcription and subsequent long-term neuroadaptations related to drug seeking behavior. Overexpression of a nuclear-localized HDAC5 in the NAc reduces both cocaine and heroin seeking following drug self-administration. However, the role and regulation of HDAC5 in critical motivational NAc afferents, such as the mPFC, has not been investigated. The goal of these studies is to examine drug-mediated regulation of HDAC5 in mPFC subregions and the functional role that HDAC5 plays in drug acquisition and seeking behaviors.

Methods: To test the functional role of HDAC5 in drug seeking behaviors, we employed a preclinical model of drug-use, rodent intravenous drug self-administration. Prior to self-administration, rats were intracranially infused with viral vectors expressing a nuclear-localized HDAC5 mutant or control in the PrL cortex and subsequently underwent cocaine self-administration, a week of forced abstinence, and extinction and reinstatement tests. To assay the effect of an abstinence period on these behaviors, a separate group of rats underwent extinction tests after only 24 hours of abstinence. To examine how cocaine may regulate HDAC5 subcellular localization, we immunohistochemically examined HDAC5 distribution following non-contingent drug administration by comparing cytoplasmic to nuclear expression. Ongoing studies using chemogenetic regional- (PrL) and pathway- (PrL-NAc) specific manipulations are aimed at understanding the role of the PrL in drug-seeking on extinction day one and following cue-induced reinstatement, adding to the previous pharmacological and optogenetic assays of this question.

Results: We found that the overexpression of nuclear HDAC5 in the PrL cortex (but not a separate subregion of the mPFC, the infralimbic cortex) reduced cocaine-seeking on Extinction Day 1, but not cue- or cocaine-primed seeking. We hypothesized that nuclear-HDAC5 was preventing abstinence-mediated changes in transcription that later contributed to the reduction in drug-seeking on Extinction Day 1. However, we found that nuclear-HDAC5 significantly suppressed Extinction Day 1 seeking even after only 24 hours of abstinence. We then sought to understand how cocaine is regulating HDAC5 in the PrL cortex. Our preliminary evidence indicates that following non-contingent cocaine injections, cocaine alters HDAC5 subcellular localization in the PrL cortex in comparison to saline-injected controls. Ongoing studies examining the role of the PrL in drug-seeking on Extinction Day 1 indicate the importance of pathway-specific manipulations, and will contribute to our interpretation of nuclear-HDAC5's specific reduction of drug-seeking on Extinction Day 1.

Conclusions: Our findings suggest that nuclear HDAC5 suppresses drug-seeking in a region- and relapse modality-specific manner, and in the PL, it suppresses seeking behavior independent of a function during extended abstinence. As such, nuclear HDAC5 might block formation of specific memories linking the drug taking context (but not discrete cues) to drug reward. Ongoing and planned studies are aimed at understanding the specific neural circuits underlying drug-seeking on Extinction Day 1, and how nuclear HDAC5 in the PrL cortex interfaces with input-specific plasticity processes that encode drug memories and regulate drug seeking behavior. Our findings contribute to the understanding of drug-mediated epigenetic alternations in motivationally relevant structures, and the functional contribution of a specific epigenetic enzyme, HDAC5, to drug-seeking behaviors.

Keywords: Epigenetics, mPFC, Drug Addiction, HDAC5, Extinction

Disclosure: Nothing to disclose.

T163. Sex Differences in the Responsiveness of Rat NAc Astrocytes to Cocaine Self-Administration

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Background: Neurobiological adaptations in the nucleus accumbens (NAc) following withdrawal from drug use are associated with vulnerability to relapse. Among the identified changes in the NAc is decreased expression of the glutamate transporter GLT-1. Because GLT-1 is primarily expressed on astrocytes, an important and related question emerges regarding what other adaptations occur in astrocytes following drug use. Recent studies indicate that short-access (ShA) cocaine self-administration and extinction training in rats leads to a decrease in the surface area, volume, and synaptic colocalization of NAc astrocytes (Scofield et, 2016; Testen et al., 2018). However, it is currently unknown if these findings extend to other preclinical models of cocaine self-administration, such as the incubation of cocaine craving model. Moreover, it is unknown if the changes in NAc GLT-1 expression and/or astrocytes are observed in female rats.

Methods: To address these questions, high-resolution confocal imaging of NAc astrocytes was performed following long-access (LgA, 6-hours/day) cocaine self-administration followed by 45 days of abstinence, in both male ($n = 10$ saline; $n = 10$ cocaine) and female ($n = 12$ saline; $n = 12$ cocaine) rats. The structural complexity of NAc astrocytes was further assessed using a branching pattern analysis. The peripheral processes of astrocytes were traced in order to construct a high-fidelity wire model. Individual wire models were then analyzed by a custom-made MATLAB script, capable of mapping and classifying individual branching nodes, as well as performing a Scholl analysis. For all astrocyte imaging data, a nested ANOVA was used for statistical analysis. For assessment of GLT-1 expression, similarly to previous studies that characterized changes in NAc GLT-1 expression in male rats following LgA/abstinence (Kim et al., 2018; Fischer-Smith et al., 2012), NAc GLT-1 protein and mRNA levels were assessed in female rats using Western blot ($n = 16$ saline; $n = 15$ cocaine) and qPCR ($n = 17$ saline; $n = 22$ cocaine). For both Western blot and qPCR data, a two-tailed unpaired *t*-test was used to conduct statistical analysis.

Results: Results indicate that following LgA/abstinence, astrocytes in the NAc of male rats show marked decreases in surface area, volume and colocalization with the post-synaptic marker PSD-95 ($p < 0.05$). However, these changes were not observed in female rats. Furthermore, in male rats, the branching complexity of NAc astrocytes was significantly decreased following LgA/abstinence ($p < 0.05$). Importantly, compared to the changes in branching complexity following ShA/extinction, this decrease in branching complexity is more pronounced following LgA/abstinence. Moreover, despite known decreases in GLT-1 subsequent to cocaine self-administration in male rats, NAc GLT-1 expression was not downregulated following LgA/abstinence in female rats.

Conclusions: These results indicate sex differences in the cocaine-induced changes in NAc astrocytes. In male rats, NAc astrocytes exist in an atrophic state following prolonged abstinence from LgA cocaine self-administration, associated with decreased synaptic colocalization. This retracted phenotype signifies a cellular adaptation that occurs during abstinence and may have implications for synaptic correlates of cocaine incubation. However, in female rats, other mechanisms and cellular adaptations may contribute to the incubation of cocaine craving. These results also indicate that in male rats, compared to ShA/extinction, the changes in NAc astrocytes are more extensive following LgA/abstinence. This includes greater decreases in surface area, volume, synaptic co-localization and branching complexity of NAc astrocytes. These results also highlight a correlation between the cocaine-induced changes in NAc astrocytes and the cocaine-induced downregulation in NAc GLT-1 expression. Whereas male rats show changes in NAc astrocytes and GLT-1 expression that are more pronounced following LgA/abstinence, none of these changes are observed in female rats. Whether this relationship is merely correlational or mechanistically linked remains to be studied.

Keywords: Astrocytes, Cocaine Self-Administration, Cocaine Sex Differences, GLT-1

Disclosure: Nothing to disclose.

T164. A Shared Epigenetic Modulator Between Sexes that Drives Adult Anxiety After Adolescent Alcohol Exposure

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Background: Adolescent alcohol exposure increases the risk 5-7 times of developing an alcohol use disorder (AUD) or psychiatric disorder later in life. Individuals with AUD are 40–60% likely to also have a comorbid anxiety disorder. However, the exact molecular mechanisms that drive either anxiety or alcohol use disorder are still poorly understood. We recently discovered that the epigenetic enzyme enhancer of zeste homolog 2 (EZH2) is involved in epigenetically remodeling the synaptic activity response element (SARE) of the activity-regulated cytoskeleton associated protein (Arc) in the amygdala of individuals with AUD who began drinking before the age of 21. Here we used a rat model of adolescent intermittent alcohol exposure (AIE) that has recapitulated an anxiety-like phenotype to determine the role of EZH2 in mediating changes that are produced by adolescent alcohol exposure and persist until adulthood.

Methods: prague Dawley rats from both sexes were given either intermittent (2days on/off) ethanol (2g/kg, AIE) or saline (0.9% NaCl, AIS) from postnatal day 28 to 41 then allowed to grow to adulthood (PND 92 to 112). Rats then underwent stereotaxic surgery and were bilaterally cannulated to central nucleus of the amygdala (CeA). Following one week of recovery, rats were infused with either a negative control siRNA or an siRNA specific to EZH2 then 24hrs later assessed in elevated plus maze (EPM). Following anxiety-like behavior, brains were collected for evaluation of mRNA (qPCR), chromatin immunopreciptations (ChIP) or gold-immunolabeling using standard methods.

Results: We evaluated if there were regional differences in expression of EZH2 after AIE in the amygdala. We found using gold immunolabeling that EZH2 is increased in both the CeA and medial nucleus of amygdala (MeA) of both sexes in AIE treated rats ($p < 0.001$, $n = 5$/group) and that knockdown of EZH2 prevents this increase. Since we have previously demonstrated in human postmortem amygdala that EZH2 is involved in regulating ARC expression, we evaluated Arc mRNA using qPCR and found that EZH2 knockdown in the CeA prevents decreases in Arc in both sexes ($p < 0.001$, $n = 6$–8/group). Our results in human postmortem brain suggested that EZH2 controls ARC expression by depositing repressive H3K27me3 at the ARC synaptic activity response element (SARE) site, so we used ChIP assays to determine if this occurred in rats as well. In both sexes, there was an increase in H3K27me3 at the Arc SARE following AIE ($p < 0.001$, $n = 5$–7/group) and increased binding of EZH2 ($p < 0.001$, $n = 5$–7/group) which was prevented by the infusion of EZH2 siRNA ($p < 0.001$, $n = 5$–7/group). To determine if these changes had functional consequences on protein expression, we evaluated Arc in the CeA and found that EZH2 knockdown in the CeA prevents decreased Arc protein expression in the CeA ($p < 0.001$, $n = 5$/group). In addition, we observed that in both male and female rats, knockdown of EZH2 prevents heightened anxiety-like behavior as measured by the EPM ($p < 0.0001$, $n = 6$–7).

Conclusions: Our results indicate that EZH2 is dysregulated in both adult male and female rats in the CeA that have been

exposed to ethanol during adolescence. AIE-induced changes EZH2 cause epigenetic remodeling at the Arc SARE that result in decreased Arc expression which can be reversed by the knockdown of EZH2 in the CeA. Knockdown of EZH2 in the CeA also prevents anxiety-like behavior induced by AIE in adulthood. Taken together these results demonstrate a shared epigenetic target between the sexes that contributes to adult psychopathology after adolescent alcohol exposure. This suggests that EZH2 may be a potential target for the treatment of early onset alcohol use disorders and associated anxiety behaviors (Supported by NIH-NIAAA P50AA022538, UO1AA019971, U24AA024605 and by the VA Merit and Senior Research Career Scientist award to SCP and F32AA027410 to JPB).

Keywords: Epigenetics, Alcohol and Substance Use Disorders, Adolescent Anxiety, Sex Differences

Disclosure: Nothing to disclose.

T165. D1R-MSN Specific Role of HDAC3 Within the NAc in Regulating Cocaine-Induced Plasticity

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Background: Cocaine utilizes mechanisms of synaptic plasticity and transcription within the nucleus accumbens (NAc) to promote drug-seeking behaviors. Recent work from the field demonstrates that this occurs in a cell-type specific manner, often differentially affecting mechanisms of plasticity within the two major output cell types of the NAc: dopamine D1- (D1R) vs D2-receptors (D2R) medium spiny neurons (MSNs)1–3. Consistent with this, activation of D1R- and D2R- MSNs drive opposing behavioral responses to cocaine4. However, it is unclear how cocaine affects epigenetic mechanisms within D1R- vs D2R- MSNs to promote cocaine-associated behaviors5,6. Prior work from our lab demonstrates that the histone deacetylase 3 (HDAC3) is a critical negative regulator of cocaine-induced gene expression and cocaine-associated memory formation7,8. Thus, we hypothesized that HDAC3 plays a cell-type specific role in the NAc that regulates responses to cocaine.

Methods: First, we examined the role of HDAC3's deacetylase activity by globally overexpressing a deacetylase-dead HDAC3 point mutant (HDAC3-Y298H-v5) using AAV vectors in the NAc of mice. With this approach, we tested the role of HDAC3 activity in regulating cocaine-induced gene expression, synaptic plasticity and behaviors. In subsequent studies, using Cre-dependent viral vectors of HDAC3-Y298H-v5 in combination with D1R- and D2R-Cre driver mice, we studied how cell-type specific manipulations of HDAC3's activity within the two major cell types of the NAc affects molecular, cellular and behavioral response to cocaine.

Results: We found that globally disrupting HDAC3's deacetylase activity altered cocaine-induced changes in gene expression and synaptic plasticity, Expression of the transcription factor Nr4a2 was particularly affected ($p = 0.0024$) and reversed cocaine-induced changes in synaptic plasticity within the NAc, ($p = 0.0032$). However, global overexpression of HDAC3-Y298H-v5 had no effect on cocaine-induced behaviors, including cocaine-conditioned place preference ($p = 0.565$). These findings suggested that there may be differential roles of HDAC3 within the cell types of the NAc. Following this, we observed the expression profile of HDAC3 following cocaine exposure within these two MSN cell types Next, we found that D1R-, but not D2R-MSNs, enhances cocaine-induced conditioned place preference in both males and females. D1R-MSN specific disruption of HDAC3 activity also altered cocaine-seeking following intravenous cocaine self-administration.

Conclusions: Together, these results illustrate how cocaine alters mechanisms of histone acetylation to induce cell-type specific changes in plasticity to regulate drug-associated behaviors.

Keywords: Epigenetics, Cocaine, Nucleus Accumbens

Disclosure: Nothing to disclose.

T166. Afferent-Associated Morphological Plasticity of Astrocytes in the Ventral Pallidum After Heroin Self-Administration

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Background: GABAergic projections from the nucleus accumbens core (NAcore) to the dorsolateral ventral pallidum (dlVP) are necessary for reinstated cocaine seeking induced by cocaine-associated cues. While the dlVP receives input from both D1 and D2 receptor expressing medium spiny neurons (MSN) in the NAcore, D2 MSN projections inhibit motivated behavior, including cued drug seeking, and exhibit enhanced LTD after chronic cocaine use and withdrawal1. Astrocytes are situated perisynaptically and are capable of uptake and release of both GABA and glutamate and are therefore capable of modulating synaptic physiology. Moreover, astrocytes in the NAcore have been shown to exhibit cue-induced morphological plasticity that attenuates heroin seeking.

Methods: In order to study the contribution of astrocytes to synaptic plasticity in the dlVP, we examined astroglial proximity to the synaptic marker synaptojanin 1 (synj1) and astroglial expression of the GABA transporter GAT-3 in the dlVP using confocal microscopy after extinction from heroin self-administration and during reinstated seeking. We also examined whether astroglial adaptations induced by heroin use and withdrawal were associated with D1 or D2 MSN terminals in the dlVP.

Results: We found a constitutive upregulation of GAT-3 in dlVP astrocytes after extinction from heroin self-administration that co-registered with synj1, but was not selectively associated with D1 or D2 terminals. During 15-min of exposure to heroin-associated cues, elevated lever pressing coincided with a reduction in GAT-3 co-registration with synj1, despite no change in synj1 expression overall. Interestingly, astrocyte proximity to D1 terminals was increased during heroin extinction, but returned to baseline levels during 15-min of cued heroin seeking. The same association was not observed at D2 terminals.

Conclusions: Our findings demonstrate that astrocyte processes exhibit morphological plasticity in a pathway-selective manner within a single brain region.

Keywords: Astrocyte-Neuron Interaction, GAT-3, Ventral Pallidum

Disclosure: Nothing to disclose.

T167. Mom Power Parenting Treatment for Substance Use Disorders and With Online Groups

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Background: Rooted in Attachment Theory and trauma-informed clinical work, Mom Power (MP) is an evidence-based, manualized, 13-session (10 group + 3 individual) intervention delivered across 12-weeks. MP was developed as a

transdiagnostic intervention for mothers of infants and toddlers (<age 3) exposed to a broad range of adversities, including postpartum depression, interpersonal trauma (childhood or as an adult), post-traumatic stress disorder (PTSD), social isolation, young age, and poverty. MP improves sensitive caregiving, parental stress and depression. MP targets emotion regulation and promotes maternal reflective function, correcting distorted parenting beliefs, improving parenting sensitivity, and reducing depression, anxiety and stress. In addition, MP counteracts social isolation by capitalizing on peer group structure with facilitated group activities and tight case management. We have evidence that that MP modulates maternal brain responses to own-baby cry and own-child mirroring, that are important for maternal sensitivity, according to stress. However, MP has not been even been established to be feasible for mothers with substance use disorders (SUD) or during pandemic circumstances. The United States is currently amid an Opioid Use Disorder (OUD) epidemic for pregnancies, with incidence quadrupling from 1999 to 2014. Subsequent parenting, a key determinant of human health, is adversely affected by OUD and commonly comorbid SUD. Even with current "gold standard" medication assisted therapies such as buprenorphine treatment (BT) to prevent withdrawal, mothers with BT/OUD are at high risk for relapse and associated problems of stress, depression, polysubstance use and maladaptive parenting behaviors that can lead to child maltreatment, costly foster care utilization and adverse child developmental outcomes. Barriers to in-person attendance for therapy, which are particularly serious for postpartum mothers, are compounded during pandemics, such as the currently with COVID-19. Effective additional treatments for mothers with SUD are sorely needed.

Methods: We conducted two pilot studies. First, we studied MP among women with SUD (45% OUD), using a pilot pre/post-design. Of the 30 women recruited, $N = 21$ (attrition 30%) completed the program and provided post-intervention data on depression, PTSD and self-rated usefulness. Second, we piloted a MP-virtual version for non-OUD high risk mothers utilizing an iterative process and incorporating feedback from participants and providers. Core components of MP are retained, such as the 3 individual and 10 group session format delivered across 12 weeks, and the weekly brief phone encounters for case management. However, all sessions were delivered virtually through videoconferencing, and recorded. An additional feature for the virtual version, is a facilitated social media interaction, by which group facilitators moderate a closed Facebook group for participants and encourage communication outside of group sessions. Group facilitators also post activities and questions related to the curriculum each week, and actively invite (and incentivize through weekly prize drawing) mothers to participate in group chat. Social media features were added based on feedback from participants.

Results: First for mothers with SUD, MP graduates improved significantly in depressive symptoms (Edinburgh Postnatal Depression Scale, EPDS, score range 0–30; > 13 probable clinical depression) with a pre/post change of 4.84 ($t = 3.29$, $p < .05$). Also, PTSD symptoms (National Women's Study PTSD Module NWS-PTSD, score range 0–17) improved with a pre/post change of 2.75 ($t = 1.75$, ns). Finally, participants rated the pilot intervention as useful for gaining parenting skills and abstaining from substances, although craving ratings and urine drug tests were not performed. With the virtual curriculum, preliminary results suggest satisfaction was high (90+% "strongly agree/agree" that MP virtual was helpful and feasible).

Conclusions: Mothers with SUD, including OUD, can be recruited and provided MP parenting intervention. Preliminary results suggest that MP works to reduce stress and anxiety symptoms for mothers with SUD. MP also helps with parenting skills, reduces SUD relapse risk factors and may affect substance use and child development outcomes. A virtual online curriculum for MP parenting intervention is also helpful and feasible. These results are consistent with established benefits of MP for non-OUD groups on sensitive caregiving, parental stress and depression; and reports that MP modulates maternal brain responses according to reduced stress, to own-baby cry and during empathic mirroring with own-baby pictures. Further work is needed to establish brain-based therapies for addition to medication assistant therapy for mothers with SUD.

Keywords: Substance Abuse Disorders, Psychotherapy, Maternal Depression, Parenting Distress, Posttraumatic Stress Disorder

Disclosure: Nothing to disclose.

T168. Longitudinal Effects of Acute Cannabis Exposure on Automobile Driving Behavior in a Naturalistic Simulated Environment

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Background: Driving is a complex day-to-day activity that employs a variety of cognitive and psychomotor functions in harmony, many of which are known to be affected acutely by cannabis (CNB) intoxication which could in turn pose a significant public health risk. The recent legalization of both recreational and/or medicinal marijuana in several states has thus created an urgent need to better understand the effects of CNB on such functions in the context of driving. The present study employs a longitudinal, double-blind, placebo- 2 x active dose study to investigate the effects of CNB on a variety of driving-related behaviors in a controlled, naturalistic simulated environment. Although the study involved brain imaging, the current analysis focuses only on driving behaviors.

Methods: The current study employed $N = 37$ subjects ($N = 25$ male, frequent cannabis users, mean age 24.25 + 7.01), each exposed to a placebo, low and high dose of CNB on three separate days. On each day, following a single acute inhaled 0.5 g dose of either 0%, 8% or 13% THC from NIDA-supplied dried cannabis flower via a desktop vaporizer, subjects drove a virtual driving simulator (RTI Sim Vehicle platform) three times inside an MRI scanner and once out of scanner, randomized, and dispersed throughout an eight-hour daily period. During each driving session a three distinct real-time behavioral tasks corresponding to lane-keeping following simulated wind gusts, lead car following, and safe overtaking were assessed and computed using custom Matlab scripts. Data were analyzed using a mixed model framework in SPSS v24 which included dose, session, instrument (desktop v MRI), dose*session, dose*instrument and session*instrument as primary factors, covarying for age and sex.

Results: Intoxicated subjects made significantly fewer gas pedal corrections ($p < 0.02$) during the car following task and similarly fewer corrections to the steering reversal rate ($p < 0.02$) during the lane weaving task, suggesting reduced awareness under the influence of cannabis. In addition we found that several variables showed significant differences in terms of estimates captured throughout the day suggesting that overall risk taking lessened as the day progressed and CNB effects wore off. Also, data trends suggested that under the high dose subjects took longer to return to baseline from their impaired driving patterns. Key metrics that showed such significant session effects included mean headway ($p < 0.001$) and time to collision ($p = 0.02$) from the car following task, deviation of lane position ($p = 0.03$) from the lane weaving

task, median gap ($p = 0.02$) and overtaking speed ($p = 0.02$) from the overtaking task. Although many driving measurements differed depending on whether driving was done in MRI or at a desktop setting, these differences had no relationship to different drug dose levels.

Conclusions: In summary, key driving functions affected under higher doses of CNB largely agreed with the current cross sectional literature. In general, daily variations in driving behavior suggest that most of the impaired driving took place within 3 hours after drug exposure, which might have important implications for real life driving situations. Our preliminary analyses yield numerous metrics that changed throughout the day, suggesting broad-based impairment on many metrics commonly used to quantify driving performance and risk.

Keywords: Cannabis Use, Simulated Driving, Acute Effects, Public Health

Disclosure: Elsevier- Schiz Res. Deputy Editor: Advisory Board (Self); Cannabinoid Medicine Studies: Consultant (Self)

T169. Social Information Processing in Substance Use Disorders: Insights From an Emotional Go-Nogo Task

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Background: Social function abnormalities are both a risk factor and a result of Substance Use Disorder (SUD). Accordingly, social information processing (SIP) deficits in SUD range from impaired perception of emotion in faces to impaired perspective taking. Of interest is probing SIP in SUD in the context of the increased impulsivity common in persons with SUD.

Methods: We administered an emotional go-nogo task (EGNG) to 31 individuals with Cocaine Use Disorder (CoUD), 31 individuals with Cannabis Use Disorder (CaD), 79 individuals with Opioid Use Disorder (OUD), and 58 healthy controls. Participants were instructed to respond to emotional faces (Fear/Happy) and withhold responses to expressionless faces in some task blocks, with the reverse instruction in others.

Results: Emotional faces generally elicited more approach behavior. First, emotional face targets elicited faster RT and higher hit rates in all groups, with the exception of slower RT and reduced hits to fearful faces as targets in OUD. Second, emotional faces as non-targets elicited more "false alarm" commission errors, especially in CaUD participants. False alarms were greater in CoUD participants than in age/sex-matched controls in most task conditions, with no differences in hit rates or RT. Across all participants, each of SUD group and attentional bias toward fearful face targets (faster RT relative to expressionless face targets) correlated with anxiety symptomatology after controlling for age and sex.

Conclusions: These data indicate differences in SIP between persons with SUD as function of substance of choice, and reflect earlier findings suggestive more mood symptomatology in OUD and more motor impulsivity in CoUD.

Keywords: Impulsivity, Social Attention, Substance Use Disorder, Signal Detection, Social Processing

Disclosure: Nothing to disclose.

T170. Ventral Pallidum GABA Neuron Activity is Necessary and Sufficient for Cue-Induced Reinstatement of Opioid Seeking After Voluntary Abstinence

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Background: Opioid addiction is a chronic relapsing disorder, and brain circuits involved in relapse are still poorly understood. Addicted people often cease their drug use due to mounting life consequences, only to succumb to temptation when encountering cues and contexts previously associated with drug use. Such self-imposed abstinence, despite its prevalence in the addiction cycle, is rarely modeled in rodent addiction experiments. However, prior studies in rats have shown that distinct neural circuits are involved in reinstatement of drug seeking after voluntary, relative to involuntary abstinence. We and others have shown that ventral pallidum (VP), and specifically VP GABAergic (VP GABA) neurons, mediate highly motivated reward seeking, as is characteristic of addiction. Here, we tested the functions of these neurons in a translationally-relevant model of relapse to opioid seeking after voluntary abstinence.

Methods: Male and female GAD1:Cre rats and wildtype littermates were implanted with jugular catheters and infused with Cre-dependent inhibitory Gi-coupled DREADDs ($n = 13$; AAV2-DIO-hM4Di-mCherry), excitatory Gq-coupled DREADDs ($n = 13$; AAV2-DIO-hM3Dq-mCherry), or a control vector ($n = 16$; AAV2-DIO-mCherry) into VP bilaterally. Rats were trained to lever press for i.v. remifentanil (1.9 µg/50 µL), a short-acting µ opioid receptor agonist, for 14 days in a specific ("safe") context. Drug was administered coincident with a light/tone cue during training. Next, rats were moved to a distinct "punishment context", where presses yielded remifentanil+cues, but also a 50% chance of co-administered footshock. Footshock intensity began at 0.30 mA on session 1, and was increased by 0.15 mA each day until abstinence criterion was met (<25 active lever presses on 2 consecutive sessions). After achieving abstinence criterion in the punishment context, we tested how VP GABA DREADD inhibition or activation affected remifentanil seeking by administering counterbalanced 5 mg/kg CNO and vehicle injections 30 min prior to the following tests: 1) safe context with and 2) without response contingent cues and 3) punishment context with and 4) without response contingent cues. In the same rats, we also tested VP GABA inhibition and stimulation effects on remifentanil self-administration. Data were analyzed with mixed model ANOVAs with Tukey posthocs, or *t*-tests as appropriate.

Results: We found bidirectional effects of VP GABA neuron manipulations on reinstatement behavior, in that engagement of Gi-DREADDs attenuated remifentanil reinstatement ($p < 0.05$) whereas engagement of Gq-DREADDs augmented reinstatement ($p < 0.05$). Notably, reinstatement effects were dependent upon the presence of discrete, response-contingent cues, with no effects of VP GABA neuron manipulations observed during context-only reinstatement tests. We also show that Gq-stimulation of VP GABA neurons increased reinstatement even in the punishment context that was previously paired with footshock.

Conclusions: Our results show that chemogenetic VP GABA neuron inhibition reduced remifentanil reinstatement, whereas chemogenetic stimulation augmented reinstatement, likely by influencing the salience of discrete drug-paired cues. These results reveal a novel necessary and sufficient role for VP GABA neurons in translationally-relevant opioid seeking during relapse.

Keywords: Opioid Addiction, Punishment, Reinstatement

Disclosure: Nothing to disclose.

T171. Contributions of Opioid Receptors to Striatal Dopamine Release During Naloxone Precipitated Withdrawal

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Background: There are more than 40000 annual fatalities in the United States due to opioid overdoses. The non-selective opioid antagonist naloxone is an effective intervention for preventing overdose fatalities in opioid use disorder (OUD). Naloxone antagonizes the effect of opioids on brainstem mu opioid receptors (MORs) and restores breathing rhythms in opioid-induced respiratory depression. Naloxone can also precipitate withdrawal (NPW) in OUD individuals, which is a highly aversive condition. Kappa opioid receptor (KOR) and MOR directly and indirectly affect dopamine (DA) neurons in the midbrain, but KOR could also affect striatal DA terminals. It is not known whether striatal DA release during NPW is affected by opioid receptors in the striatum. To address this, we studied the association between pattern of striatal DA release during NPW and the striatal distributions of MOR and KOR.

Methods: This study involved a retrospective analysis of 4 imaging datasets which included 50 PET sessions, collected on a total of 40 participants. All participants provided written informed consent. OUD participants ($n = 10$, 10 males, mean age = 41 years) had at least one-year history of continues opioid use (heroin or methadone) and met DSM-IV criteria for opioid dependence. OUD participants underwent two consecutive [11C]raclopride-PET imaging sessions to measure D2/3 receptor (D2/3R) availability. The first scan was performed following IV administration of 3 ml saline (SAL) and the second session was performed after 2 hours with IV administration of naloxone (NAL) in 0.1 mg/kg increments (every 4 min) until withdrawal symptoms appeared. Average percent change in D2/3R availability from NAL to SAL conditions was estimated across OUD participants to index NAL-DA release within each cubic striatal subregion (6-mm isotropic). NAL-DA release across striatal subregions was compared to baseline MOR availability measured with [11C]carfentanil-PET ($n = 10$, 6 males, mean age = 34 years), KOR availability measured with [11C]-LY2795050 ($n = 10$, 10 males, mean age = 29 years), and D2/3R availability measured with [11C]raclopride-PET ($n = 10$, 10 males, mean age = 30 years), all in healthy controls.

Results: NPW resulted in a significant increase in DA release predominantly in the dorsal striatum (pFWE < 0.05). Across striatal subregions ($n = 70$), MOR and KOR availability were highly correlated ($r = 0.8$). 3R availability/3R availability was not associated with MOR or KOR availability across striatal subregions ($p > 0.3$). Pattern of NAL-DA release across striatal subregions was not significantly associated with baseline D2/3R ($p = 0.6$) but was negatively associated with MOR ($r = -0.62$, $p < 0.0001$) and KOR availability ($r = -0.81$, $p < 0.0001$). Follow up analyses showed that only striatal KOR availability remained significantly associated with the pattern NAL-DA release after accounting for MOR and D2/3R availability ($p < 0.0001$), where KOR accounted for an additional 24% of variance in NAL-DA release across the striatal subregions ($p < 0.0001$).

Conclusions: We document that pattern of striatal DA release during NPW was inversely associated with MOR and KOR distributions in the human striatum. The unique association between NAL-DA release pattern and KOR was consistent with the direct action of KOR on striatal DA terminals. In comparison, MOR in the striatum may have an indirect role on DA terminals through its action on striatal GABAergic interneurons. While much attention has been given to the role of MOR in OUD, our findings highlight that KOR is likely an important contributor to DA release during NPW in the striatum, a key region in rewarding and aversive responses to opioids and their withdrawal. The findings could be relevant for the clinical management of acute opioid withdrawal.

Keywords: Opioid Addiction, Mu-Opioid Receptors, Kappa Opioid Receptors, Stress-Induced Dopamine Release, Opioid Withdrawal

Disclosure: Nothing to disclose.

T172. Neurofunctional Domains in Alcohol Use Disorder Predict Multiple Adverse Outcomes Linked to Addiction

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Background: The Addictions Neuroclinical Assessment (ANA) is a framework for assessing the heterogeneity of addiction, focusing on the three domains of negative emotionality, executive function, and incentive salience. We recently validated a three-factor model corresponding to the ANA domains in a diverse clinical sample and found the three factor domains to be highly correlated with one another, suggesting that relationships of the domains to addiction-related outcomes may involve both shared and specific effects. Here, we assessed the dimensionality of the three-factor structure of the ANA model using a bifactor latent variable model, in which all items load onto a broad general factor as well as specific factors. We then investigated associations of the general and specific factors with a broad spectrum of addiction-related adverse outcomes using structural equation modeling.

Methods: Participants included 1038 individuals (612 males, 426 females) ranging from non-drinking healthy volunteers to heavy drinkers diagnosed with alcohol use disorder (AUD, $n = 493$). Participants were assessed on measures of impulsivity, ADHD, personality, aggression, negative affect, and items related to thoughts and desires to consume alcohol, which provided indicator measures for the bifactor analysis that mirrored those used in the previously validated three-factor model. Assessment of adverse outcomes included recent alcohol consumption (Timeline Follow-back), alcohol use disorder severity (Alcohol Use Disorders Identification Test), smoking status, current life stress (Perceived Stress Scale), quality of life (World Health Organization Quality of Life), sleep (Pittsburgh Sleep Quality Index), pain (self-rating scale), suicidal behavior (Columbia Suicide Severity Rating Scale) and psychiatric disorders (Structured Clinical Interview for DSM-IV or DSM-5). Bifactor analysis and structural equation modeling were conducted in Mplus version 8.

Results: A bifactor model encompassing a general factor and three specific factors of negative emotionality, executive function, and incentive salience, provided good fit to the data (RMSEA = 0.06, CFI = 0.96, TLI = 0.94). Structural equation models adjusted for age, sex, and race, indicated that the general factor was significantly associated with all adverse outcomes. Specifically, the general factor was associated with increased alcohol consumption and AUD severity, higher perceived stress, self-rated pain, and sleep impairment, reduced quality of life, being a smoker, increased risk for current AUD, anxiety, mood, and other substance use disorders, and a history of suicidal thoughts and attempts. Some associations of the specific factors with adverse outcomes were still observed after accounting for the general factor, especially for measures of stress, quality of life, problem drinking, and co-morbid anxiety.

Conclusions: Our analyses suggest that the ANA be viewed as a multidimensional framework, with a broad general domain as well as more specific domains of negative emotionality, executive function, and incentive salience. These domains are clinically relevant to addiction in that they exert both shared and specific effects on adverse outcomes that are linked to addiction severity and comorbidity. These findings highlight the value of the ANA for assessing heterogeneity in the presentation and severity of addictive disorders, including AUD, and providing information that can be used to improve prevention and treatment.

Keywords: Alcohol and Substance Use Disorders, Addiction, Clinical Neurobiology

Disclosure: Nothing to disclose.

T173. Noradrenergic Dysfunction and Distinct Neural Correlates of Recent Cocaine Use and Tonic Cocaine Craving: Neuromelanin and Functional Brain Imaging

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Background: Although not as thoroughly investigated as dopamine (DA), norepinephrine (NE) has also been consistently implicated in cocaine-related reward processing (Freeman et al., 2005; Freeman et al., 2008; Platt et al., 2007; Ventura et al., 2007; Weinshenker and Schroeder, 2007). For instance, in squirrel monkeys trained to stability for operant self-administration of cocaine and then extinguished for drug seeking, priming of NE transporter (NET) inhibitors reinstates drug seeking behavior (Platt et al., 2007; see Weinshenker and Schroeder, 2007 for a review). In rodents, noradrenergic agents have a robust effect on the reinstatement of stimulant seeking (Weinshenker and Schroeder, 2007). Also notable is a study demonstrating that NET genetic polymorphism modulates subjective mood responses to d-amphetamine in healthy individuals (Dlugos et al., 2007). Although their functional consequences have yet to be substantiated, the polymorphisms are located at the transcription factor binding sites and thus likely to regulate the expression of NET gene. Relatively little is known about the effects of prolonged stimulant use on noradrenergic neurotransmission. Post-mortem and animal studies provided evidence in support of up-regulation of NET after prolonged cocaine exposure (Beveridge et al., 2005; Macey et al., 2003; Mash et al., 2005). Our recent studies similarly demonstrated that NET is up-regulated in humans addicted to cocaine (Ding et al., 2010) (Ding et al., 2010). Thus, many studies have implicated noradrenergic (NA) dysfunction in cocaine addiction. In particular, the NA system plays a central role in motivated behavior and may partake in the regulation of craving and drug use. Yet, human studies of the NA system are scarce, likely hampered the difficulty in precisely localizing the locus coeruleus (LC). The current study aimed to address this issue.

Methods: Here, we used neuromelanin imaging to localize the LC and quantify LC neuromelanin signal (NMS) intensity in 44 current cocaine users (CU; 37 men) and 59 non-drug users (NU; 44 men) at various thresholds of the peak. We also computed the NMS of the ventral tegmental area/substantia nigra (VTA/SN) as a contrast. We employed fMRI to investigate cue-induced regional responses and LC functional connectivities, as indexed by generalized psychophysiological interaction (gPPI), in CU. Imaging data were processed by published routines and the findings were evaluated with a corrected threshold, as in our previous work. We evaluated how these neural measures were associated with chronic cocaine craving, as assessed by the Cocaine Craving Questionnaire (CCQ), and recent cocaine use in total grams over prior month.

Results: Compared to NU, CU demonstrated higher LC NMS intensity (but no differences in VTA/SN NMS intensity) for all probabilistic thresholds defined of 50% to 90% of the peak. LC NMS intensity was not correlated with years of or recent cocaine use or CCQ score, with age, sex, alcohol and nicotine use severity, each quantified by the Alcohol Use Disorder Identification Test (AUDIT) and Fagerström Test for Nicotine Dependence (FTND). Drug as compared to neutral cues elicited higher activations of many cortical and subcortical regions, with cue activities and LC connectivity in positive correlation with recent cocaine use, with age, sex, AUDIT and FTND scores accounted for. Drug vs. neutral cues also elicited "deactivation" of bilateral parahippocampal gyri (PHG), with less deactivation and higher LC connectivity in positive correlation with the CCQ score, with age, sex, AUDIT and FTND scores controlled for in the regression.

Conclusions: The findings suggest that cocaine misuse may induce higher neuromelaning signal intensity, suggesting neurotoxic effects on the LC. Although both related to cue-elicited LC connectivity, recent cocaine use and chronic cocaine craving appeared to be associated with distinct neural processes. Together, these findings suggest noradrenergic dysfunction in cocaine misuse and multiple and potentially distinct LC circuit activities to support ill-adaptive psychological and behavioral processes central to cocaine addiction.

Keywords: Cocaine, Norepinephrine, Locus Coeruleus, Neuromelanin-Sensitive MRI, Cue Reactivity

Disclosure: Nothing to disclose.

T174. The Dynamic, Methamphetamine-Induced hnRNP H Interactome Reveals Synaptic RNA-Binding Targets Associated With Reduced Dopamine Release and Behavior

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Background: The genetic factors underlying risk for psychostimulant addiction remain largely unknown. We previously identified Hnrnph1 (heterogeneous nuclear ribonucleoprotein H1) as a quantitative trait gene and a set of 5′ UTR functional variants underlying reduced methamphetamine (MA) behavioral sensitivity and hnRNP H protein expression. Mice with a heterozygous frameshift deletion in the first coding exon of Hnrnph1 (H1 MUT) (containing the first RNA-binding domain) showed reduced MA-induced locomotor activity, reward, reinforcement, and dopamine release. H1 MUT also showed a two-fold increase in synaptosomal localization of hnRNP H and proteomic evidence for mitochondrial dysfunction.

Methods: To inform the mechanism of hnRNP H dysfunction in MA-induced dopamine release and behavior, we surveyed mRNA targets of hnRNP H via cross-linking immunoprecipitation coupled with high-throughput sequencing (CLIP-seq) in striatal tissue at baseline and at 30 min post-MA (2 mg/kg, i.p.). To integrate identification of hnRNP H targets with the impact of Hnrnph1 mutation and MA on downstream gene expression and splicing, we analyzed the transcriptome of the parallel samples used in CLIP-seq.

Results: Analysis of read distribution across gene subregions revealed enriched binding of hnRNP H in gene introns, comprising about 70% of the total distribution and confirming its role in splicing. The high precision of CLIP-seq allows us to investigate properties of hnRNP H binding sites. De novo motif discovery of significant hnRNP H-associated binding sites using the Homer database detected the top over-represented motif to be Guanine-rich. These findings are consistent with previous characterization of hnRNP H in cultured cells, supporting successful isolation of hnRNP H-bound RNAs in mouse striatal tissue. The genome-wide identification of hnRNP H targets using CLIP-seq in the mouse striatum of C57BL/6J revealed targets important for synaptic function. MA treatment induced opposite changes in binding of hnRNP H to mRNAs between H1 MUT versus WT mice. More specifically, in response to MA, an RNA target that is more likely to

show increased binding to hnRNP H in the H1 MUT is more likely to show decreased binding in WT, demonstrating a negative correlation between hnRNP H binding dynamics between H1 MUT versus WT in response to acute MA. This dominant negative relationship in hnRNP H binding to RNA target was most robust in 3'UTR targets in mRNAs that were enriched for synaptic proteins involved in dopamine release and psychostimulant excitatory synaptic plasticity. From the transcriptome analysis of parallel samples, a total of 19 genes showed a Genotype x Treatment interaction in differential expression, with 6 of these 19 genes (including Cacna2d2) overlapping with hnRNP H targets identified in CLIP-seq. Two of the six genes were the long non-coding RNA Malat1 and microRNA Mir124a, both of which are involved in regulation of genes important for synapse formation and synaptic transmission. RNA-binding, transcriptome and spliceome analysis triangulated on hnRNP H binding to 3'UTR of Cacna2d2, an upregulation of Cacna2d2 transcript, and decreased 3'UTR usage in response to MA in H1 MUT mice. Cacna2d2 codes for a presynaptic, voltage-gated calcium channel subunit that could plausibly regulate MA-induced dopamine release and behavior. Interestingly, the overlapping hnRNP H interactome and transcriptome showing the Genotype x Treatment interaction identified Unc13c and Camta1, both of which are calcium-responsive genes. Thus, multiple lines of evidence points to the modulation of calcium as likely potential mechanism that links blunted MA-induced dopamine release observed in the H1 MUT mice.

Conclusions: The cellular mechanism and factors regulating psychostimulant-induced changes in synaptic transmission are not fully known. Our characterization of the hnRNP H RNA interactome identified a potential novel role for hnRNP H in regulating transport, stability, and/or translation of mRNAs linked to excitatory synaptic transmission and psychostimulant-induced synaptic plasticity. Our study provides new insight into the rapid MA-induced cell biological adaptations that are regulated by hnRNP H and likely other RNA-binding proteins working in concert to modulate synaptic transmission. Integration of complementary gene sets from different Omic methods (interactome, transcriptome, and spliceome) can be broadly applied to the study of drug-induced RBP-RNA dynamics and discovery of functionally relevant RNA-binding targets underlying cell biological responses, adaptations, and organismal phenotypes such as behavior.

Keywords: GWAS, Amphetamine, Cocaine, Substance Abuse Disorders, Psychiatric Genetics

Disclosure: Nothing to disclose.

T175. Homer2 Phosphorylation is Necessary for the Aversive Properties of Cocaine and Alcohol

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Background: Homer2 is a post-synaptic scaffolding protein regulating the trafficking, cellular localization and function of Group 1 metabotropic and NMDA glutamate receptor subtypes. Cocaine experience induces regionally-specific changes in Homer2 expression in brain, while alcohol increases Homer2 expression throughout the extended amygdala. Importantly, these drug-induced changes in Homer2 expression are functionally relevant for both cocaine- and alcohol-induced changes in behavior as determined in studies of Homer2 null mutant mice and viral-mediated gene transfer approaches. Recent studies indicate that Homer2 is phosphorylated on S117/S216 in response to neuronal activity and calcium-calmodulin kinase II alpha (CaMKII) activation. This phosphorylation causes a rapid dissociation of mGluR5-Homer2 binding. Interestingly, (S117/216)-Homer2 is hyper-phosphorylated in the Fmr1 knock-out mouse model of Fragile X Syndrome, arguing a potentially important role for Homer2 phosphorylation in not only regulating behavioral sensitivity to drugs of abuse, but also in gating normal sensorimotor, cognitive, emotional and motivational processing.

Methods: To test this hypothesis, mice with alanine point mutations at (S117/216)-Homer2 (Homer2AA) were generated and back-crossed to a C57BL/6J background. A subset of mice were subjected to a behavioral test battery to examine for the effects of the phospho-mutation upon measures of negative affect (light-dark box, forced swim test, novel object test, elevated plus-maze), spatial learning and memory (Morris maze), sensorimotor gating (prepulse inhibition of acoustic startle), and motor co-ordination (rotarod). A second subset of mice were assayed for the affective/motivational properties of cocaine using cocaine-induced place- and taste-conditioning paradigms, while a third subset of mice were assayed for the intoxicating, rewarding and reinforcing properties of alcohol, using a variety of experimental procedures.

Results: When assayed for transgene effects upon spontaneous behavior, Homer2AA mice exhibited a hypo-anxious phenotype under elevated plus maze and light-dark shuttle-box procedures, but did not differ from wild-type controls in novel object reactivity, marble-burying or forced swim tests, acoustic startle or prepulse inhibition of acoustic startle, Morris maze or rotarod performance. No genotypic difference was observed regarding either cocaine- or alcohol-induced locomotor activity during place-conditioning, nor were differences observed for the sedative-hypnotic effects of alcohol under rotarod and righting reflex procedures. Homer2AA mice binge-drank less alcohol and sucrose than wild-type mice, but did not differ from wild-type mice in quinine consumption or alcohol intake under continuous-access procedures. Curiously, Homer2AA mice were less sensitive to the aversive properties of high-dose cocaine (30 mg/kg) in both place- and taste-conditioning studies and this "low aversion" phenotype extended also to high-dose alcohol (4 g/kg). Cocaine (30 mg/kg) dissociated mGlu5 and Homer2 in striatal lysates from wildtype, but not Homer2AA mice, as assessed by co-immunoprecipitation, suggesting a molecular basis for the deficit in aversive behaviors.

Conclusions: These findings provide new evidence that CaMKII alpha-dependent phosphorylation of Homer2 gates the negative motivational valence of both high-dose cocaine and alcohol, in a manner independent of drug-induced psychomotor activation. The apparent disconnect between the effects of the phospho-mutation upon binge alcohol intake and place-conditioning raises questions regarding the role for Homer2 phosphorylation in the motivation to self-administer drug, which will be examined in future operant-conditioning studies.

Keywords: Glutamate, Metabotropic Glutamate Receptor 5 (mglu5), Addiction, Alcoholism

Disclosure: Nothing to disclose.

T176. DNA Methylation of the Solute Carrier Family 7 Member 11 (SLC7A11) Gene is Associated With Alcohol Use Disorder and Endophenotypes Related to the Liver-Brain-Axis

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Background: Alcohol use disorder (AUD) is a chronic relapsing disorder with strong genetic, epigenetic and environmental components. Recent work of epigenetic factors related to alcohol

consumption phenotypes has robustly identified differential DNA methylation in the gene encoding the solute carrier family 7 member 11 (SLC7A11). SLC7A11 encodes the sodium-independent cysteine-glutamate antiporter known as system Xc- which is implicated in glutamate transport, lipid metabolism, liver function, and oxidative stress regulation in the brain.

Methods: To understand a potential role of SLC7A11 in AUD, we investigated the association of the CpG site cg06690548, located in the promoter region of the SLC7A11 gene, with clinical biomarkers, including liver function enzymes (LFTs) and brain volumes measured by structural magnetic resonance imaging (MRI) scans in 615 participants consisting of 372 AUD and 243 healthy controls (HC) recruited by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) at the National Institutes of Health (NIH). The methylation level of cg06690548 was accessed using an Infinium MethylationEPIC BeadChip and all association analyses were performed with logistic and linear regression models after adjusting for gender, age, and race.

Results: We found that cg06690548 was hypomethylated in individuals with AUD compared to HC ($p = 4.1E-17$) and the decreased methylation was consistently associated with heavy alcohol consumption measured by the number of drinks per day and heavy drinking days ($p < 0.0001$). Our data also showed the decreased methylation was associated with increased levels of liver enzymes, GGT ($p = 1.03E-21$), ALT ($p = 1.29E-06$), and AST ($p < 1.0E-06$), and decreased brain volumes in the hippocampus, middle cingulate gyrus and middle frontal gyrus ($p < 0.05$). These directional associations among the endophenotypes related to the liver-brain axis may provide a pathologic role of glutamate signaling disruption in AUD and associated disorders.

Conclusions: Our data further support a possible functional role of promoter DNA methylation of SLC7A11 in phenotypes related to AUD that span multiple organ systems, mainly the liver-brain axis. Given its prominent role in glutamate homeostasis, additional work is needed to elucidate the exact mechanisms by which SLC7A11 dysregulation might contribute to AUD.

Keywords: Epigenetics, Alcohol, Glutamate, Epigenome Wide Association Studies, Liver Brain Axis

Disclosure: Nothing to disclose.

T177. An Investigation of Peripheral Metabolic Biomarkers and Reward Processing in Individuals With Alcohol Use Disorder

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Background: Recent studies have highlighted the significance of the gut-liver-brain axis in alcohol use disorder (AUD) and alcohol seeking behaviors. Aspects of the gut-liver-brain axis, such as hormones, have been widely characterized as playing a role in feeding behavior, energy homeostasis, and more recently shown to modulate central reward and stress pathways related to alcohol seeking behaviors. However, the role of other aspects of the gut-liver-brain axis in reward and stress related pathways and alcohol seeking behaviors remains less explored.

Efficient and normal metabolism is required for energy homeostasis and the production of critical hormones in this system. As such, dis-regulation of metabolism or changes in metabolic factors underlying the gut-liver-brain axis may result in changes in central reward pathways and alcohol related behaviors. Studies investigating feeding behavior and obesity have revealed changes in circulating gut-liver hormones and triglycerides levels are associated with reductions in neural response to palatable food cues in brain regions regulating reward and feeding behaviors. Additionally, another study investigating the role of blood glucose levels (HbA1c) and food reward related brain activation in individuals with diabetes, found that individuals with improved HbA1c (after gastric bypass procedure) showed substantially higher activations in brain regions associated with reward compared to those with no improvements to HbA1c. Together, these findings suggest that the regulation of metabolism may play an important role in feeding and reward related pathways and may also modulate the gut-liver-brain axis and its role in these pathways.

Methods: To begin to explore the role of metabolism in the gut-liver-brain axis and reward and stress related pathways, we investigated the relationship between metabolic factors (glucose, cholesterol, and triglycerides) and reward anticipation in individuals seeking treatment for AUD. Using the Monetary Incentive Delay (MID) we assessed neural responses to the anticipation of rewards in three conditions: high reward gain, high reward loss and low reward gain and loss.

Multiple mediation analyses were used to model the association between alcohol use (measured by Alcohol Use Disorder Identification Test (AUDIT)) and neural responses to reward anticipation (MID task) in seventy-three individuals with AUD. Measures of glucose, cholesterol, and triglycerides were included as mediators in mediation models with AUDIT total score predicting reward anticipation during an fMRI version of the MID task.

Results: Triglycerides levels significantly mediated the association between alcohol use and left amygdala activity in anticipation of losing a high value reward ($p = 0.033$) while all other peripheral metabolic biomarkers did not significantly mediate any associations between alcohol use and reward anticipation.

Conclusions: In this study, triglyceride levels mediated the relationship between alcohol use and neural responses to the anticipation of losing a reward during the MID task in the left amygdala. These preliminary findings highlight the potential role of metabolism in reward and motivation pathways. Research on feeding related behavior and obesity suggests metabolic factors may play a role in responsiveness to food related cues and modulate feeding behavior and response to food related reward. Similar metabolic factors may also play a role in responsiveness to addiction related reward and may contribute to the role of the gut-liver-brain axis alcohol seeking behavior.

Keywords: Human Neuroimaging, Alcohol Use Disorder Metabolism Reward, Reward Anticipation, Metabolic Biomarker

Disclosure: Nothing to disclose.

T178. Early Life Adversity Promotes Sex-Specific Resilience to Opioid Addiction-Related Phenotypes

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Background: Opioid use disorder is on the rise and the economic and human cost is staggering. It remains unclear why only a subset of people who take opioids develop substance use disorder (SUD), prompting efforts to understand factors that promote vulnerability to opioid misuse. However, it is also critical to identify factors that promote resilience to SUD. Experiences early in life can alter risk/resilience to the later development of disorders. For example, early life stress that is not overwhelming can have an "inoculating" effect that promotes the development of resilience in adulthood. Here we use a rat model of early life adversity, the limited bedding and nesting (LBN) model, to assess how this manipulation affects addiction-like phenotypes in adulthood.

Methods: In LBN, rat dams and their pups were exposed to a low resource environment from postnatal day 2-9. When male and female offspring reached adulthood, they were tested on behaviors related to substance abuse ($n = 5–12$/group): impulsivity and drug self-administration. Impulsive choice was examined using the delay discounting task where rats can choose between a smaller/immediate vs. a larger/delayed reward. Drug taking behavior was measured using morphine self-administration and motivation for morphine was assessed with a progressive ratio (PR) reinforcement schedule. To understand how LBN could affect later behavior, we assessed changes to neuroepigenetic processes in the nucleus accumbens (NAc), which mediates both impulsivity and drug-seeking. To assesses changes in gene transcription, we performance on RNA sequencing (RNA-seq) to NAc punches ($n = 5$/group). We assessed genome-wide changes in histone modifications by measuring post-translational modifications using a HPLC-MS mass-spectrometry-based assay ($n = 4–5$/group).

Results: We first tested whether adult male and female rats with a history of LBN exposure had altered impulsive choice in the delay discounting task. LBN-exposed males more often chose the larger/delayed reward, indicating a reduction in impulsivity (interaction [$F(3,48) = 4.59$, $p = 0.007$]). LBN did not affect delay discounting in female rats. High impulsivity is associated with drug taking, but here we found LBN reduced impulsivity in males. Similarly, intake of morphine (0.25mg/kg/infusion on an FR1 schedule) was reduced in LBN vs. control males (main effect [$F1,10 = 5.974$, $p = 0.03$]). On a PR, LBN males earned fewer infusions compared to control males [$t10 = 2.44$, $p = 0.03$]. In females, LBN did not affect intake of morphine on either a FR1 or PR schedule. RNA-seq on NAc tissue revealed sex-specific changes in gene expression. Interestingly, the number of differentially expressed genes (DEGs) was higher in females than males, suggesting that high transcriptional regulation in the NAc in LBN females is required to maintain their physiology and behavior at control levels. Pathway analysis of DEGs revealed that the SNARE pathway involved in vesicular transport was significantly enriched only in males (adjusted $p = 0.01$), which could affect synaptic transmission. Finally, our analysis of histone post-translational modifications revealed that LBN significantly altered the abundance of 1 mark in females as compared to 3 permissive modifications in males. Acetylation of lysine 8 on histone 4 (H4K8ac), a mark that is often found near active promoters, was enriched in LBN vs. control males. Increased deposition of H4K8ac may partly account for many of the upregulated transcripts in LBN males.

Conclusions: Collectively, these data indicate that LBN can inoculate males against addiction-like behavioral phenotypes. These alterations in behavior are likely driven by sex-specific physiological, transcriptional, and epigenetic modifications in the NAc induced by LBN. Given that the addiction-related behavior appears unaffected by the LBN manipulation in females, comparing LBN-induced epigenetic changes in males vs. females can reveal novel mechanisms that can promote resilience to SUD, which may lead to the development of better therapies to reduce opioid misuse.

Keywords: Nucleus Accumbens, Impulsivity, Substance Use Disorders, Sex Differences, Early Life Stress

Disclosure: Nothing to disclose.

T179. Alcohol Acutely Suppresses Ghrelin Through an Indirect Mechanism – Converging Evidence From Preclinical and Clinical Data

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Background: Ghrelin is an orexigenic gastric peptide that potentiates alcohol-seeking by affecting alcohol craving, consumption, and reward processing. However, the reverse effect of alcohol intake on the ghrelin system remains to be fully understood. Literature to date demonstrates that alcohol administration can acutely suppress acyl-ghrelin in rodents and humans but the mechanism by which this occurs has yet to be evaluated.

Methods: We examined the effect of alcohol on the ghrelin system through the following experiments: (1) secondary analysis of data using linear mixed effects modeling of four human laboratory paradigms ($N = 6, 11, 12, 16$) involving intravenous (IV) and oral alcohol administration to male and female participants (2) evaluating expression changes in the ghrelin receptor, ghrelin peptide, and ghrelin acylation enzyme (GOAT) genes (GHSR, GHRL, and MBOAT4, respectively) in post-mortem samples from male individuals with alcohol use disorder (AUD) ($N = 11$) vs. non-AUD controls ($N = 16$) (3) comparing intraperitoneal (i.p.) alcohol administration in both wild-type (WT) and ghrelin receptor knockout (Ghsr KO) male rats ($N = 34$) (4) observing the effect of increasing concentrations of alcohol on acyl-ghrelin secretion from cultured gastric mucosal cells ex vivo as well as on (5) GOAT acylation activity in vitro and (6) evaluating the effects of i.p. alcohol and calorically equivalent sucrose solution on acyl and des-ghrelin in male rats ($N = 34$).

Results: Our analysis of four human laboratory experiments revealed an overall reduction of acyl- and total ghrelin following both oral and IV alcohol administration. Using linear mixed effects modeling, we observed an overall main effect of time on acyl and total-ghrelin during fixed oral alcohol administration [AG: $F(5, 53.8) = 10.5$, $p < 0.001$), TG:$F(5, 52) = 13.6$, $p < 0.001$], oral alcohol self-administration (ASA) [AG: $F(3, 27.5) = 6.6$, $p = 0.002$, TG: $F(3, 37.7) = 4.5$, $p = 0.009$], and IV-ASA experiments [AG: $F(4,37.7) = 7.5$, $p < 0.001$, TG: $F(4, 38.7) = 5.6$, $p = 0.001$], but not during a fixed-IV alcohol administration experiment [AG: $F(4,19) = 2.0$, $p = 0.134$, TG: $F(4,17.1) = 2.7$, $p = 0.067$]. Linear mixed effects models were used to evaluate the effect of group (AUD vs. control non-AUD) on GHSR, GHRL, and MBOAT4 expression in the hippocampus, ventral tegmental area (VTA), nucleus accumbens (NAc), amygdala, and prefrontal cortex (PFC). There was no significant difference in expression between groups for all genes and regions tested after controlling for multiple testing. We found an overall treatment effect (alcohol vs. saline) on acyl-ghrelin levels [$F(1,29) = 6.212$, $p = 0.019$], but not des-acyl ghrelin levels [$F(1,29) = 0.013$, $p = 0.91$] in male WT and Ghsr KO rats 15 minutes post-injection. Moreover, exposing ghrelin secreting gastric mucosal extracts to increasing concentrations of alcohol had no effect on acyl-ghrelin secretion, and increasing concentrations of ethanol did not dose-dependently inhibit GOAT acylation activity. Comparison of the effect of alcohol and a calorically equivalent sucrose solution on acyl- and des-acyl ghrelin revealed that alcohol and sucrose have different effects on each form of ghrelin. While alcohol significantly decreased acyl-ghrelin and blunted a fasting-induced increase in des-acyl-ghrelin, sucrose blunted a fasting-induced increase in acyl-ghrelin and had no effect on des-acyl ghrelin.

Conclusions: Our data from humans and rats show that alcohol acutely suppresses plasma ghrelin regardless of route of administration. Data from human post-mortem samples and Ghsr KO rats preliminarily show that this effect does not appear to be dependent on the ghrelin receptor. Moreover, we show that that ethanol does not affect GOAT acylation activity in vitro or acyl-ghrelin secretion from gastric mucosal cells ex vivo, indicating that alcohol may not suppress plasma ghrelin via directly inhibiting the ghrelin system. Lastly, we observed different effects of alcohol and sucrose despite equivalent caloric values on acyl and des-acyl ghrelin, suggesting that alcohol does not simply affect ghrelin in a

manner proportional to caloric load and may affect acyl-ghrelin and des-acyl ghrelin secretion differently.

Keywords: Ghrelin, Alcohol, Postmortem Brain Tissue, Animal Research, Human Laboratory Study

Disclosure: Nothing to disclose.

T180. Neuroimmune Underpinning of Social Factors in Cocaine Addiction

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Background: Chronic cocaine use and prolonged social stress both induce peripheral and central immune activation, while concomitantly, activation of the immune system contributes to stress-induced neural/behavioral abnormalities. Immune dysregulation may provide a psychobiological link between chronic social stress, deficits in social information processing, and addiction via activation of the sympathetic stress systems and the limbic-Hypothalamic-Pituitary-Adrenal Axis.

Methods: Blood serum of 18 individuals with cocaine use disorder (iCUD) and 19 healthy controls (HC) not differing on age, gender, race, and IQ, were compared for inflammatory or immunosuppressive cytokines, chemokines and growth factors. The same cytokine panel was examined in relation to whole-brain activation while participants performed a task of simulated social interactions (Social Navigation fMRI paradigm). Immune associations were tested with non-task variables of drug use, social stress (childhood trauma), and real-life social competencies (social-adaptive traits; personality traits were standardized and averaged to form a composite score). Testing in additional participants utilizing factor analysis (to obtain a comprehensive immune signature) is ongoing.

Results: Compared with HC, iCUD had elevated interleukin-3 [IL-3; $t(36)=-4.3$, $p < 0.001$] and platelet-derived growth factor [PDGF-AA; $t(36)=-2.3$, $p = 0.026$], and a trend for increased Macrophage-Derived Chemokine [MDC/CCL22; $t(36) = -2.0$, $p = 0.054$]. At the neural level, during simulated social interaction and relative to HC, BOLD signal in iCUD was greater in the precuneus/ventral posterior cingulate cortex (Prc/vPCC; height threshold $p < 0.005$, extent threshold $k = 20$; $X = -6$, $y = -53$, Brodmann Area = 23; $z = 3.5$; $k = 454$, pFWE-cor. < 0.024; no activation survived correction for multiple comparisons for iCUD<HC). Across our whole sample, Prc/vPCC activation correlated positively with RANTES, a pro-inflammatory chemokine (mediates T cells activations in acute and chronic inflammation; iCUD: $r = 0.614$, $p = 0.007$; whole sample: $r = 0.322$, $p = 0.052$). At the behavioral level, in iCUD, RANTES correlated positively with recency of cocaine use ($r = 0.508$, $p = 0.031$). Peripheral MDC (proinflammatory cytokine, implicated with post-trauma) correlated with childhood trauma sexual abuse ($r = 0.447$, $p = 0.006$), which was experienced to a greater extent in iCUDs [$t(36) = -3.4$, $p = 0.003$]. Proinflammatory cytokine IL-1b correlated negatively with social-adaptive traits ($r = -0.523$, $p = 0.023$), where the greater the immune dysregulation, the lower the social-adaptive traits in iCUD.

Conclusions: iCUD had heightened immune activation state which was associated with Prc/vPCC brain function during social processing, drug use, social stress, and real-life social competencies. These findings indicate a potential relationship between immune and social factors in cocaine addiction, providing a foundation for future causal testing. Delineating the peripheral and neural underpinnings of stress-related inflammatory signature in relation to psychosocial state in iCUD could advance the development of novel treatment to enhance efficacy and recovery.

Keywords: Neuroimmune Interaction, Human Neuroimaging, Social Factors and Functioning, Cocaine Addiction, Psychoneuroimmunology

Disclosure: Nothing to disclose.

T181. Open Bar Assay: A New Operant Paradigm for Examining Motivated Response and Substance Abuse in Drosophila Melanogaster

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Background: Escalation of alcohol self-administration facilitates the transition from alcohol use to compulsive drinking, which is a worldwide biomedical concern. Alcohol research has largely been focused on understanding the neural mechanisms underlying excessive or compulsive alcohol intake. However, humans display a wide-variety of drinking behaviors with some escalating alcohol consumption over time while others moderately drink or even abstain. Much less is understood of the neural substrates underlying individual differences in alcohol preference and seeking, and how escalation arises in some individuals and not others. Investigating the circuits and neural dynamics underlying this individual variation is critical for developing more effective treatments for alcohol use and abuse disorders. In Drosophila melanogaster, the neural circuits required for encoding valence include identifiable connections, genetic and/or biochemical profiles and characterized temporal changes underlying learning, making flies an ideal model for investigating escalation of self-administration.

Methods: We developed a 3-day operant paradigm to evaluate the spectrum of behaviors associated with self-administration of a pharmacologically relevant dose of volatilized ethanol (50% EtOH), and compared this to the response to naturally appetitive odors. We examined 4-5 day old male and female flies, and used a combined computer vision and machine learning approach was to evaluate subtle behavioral changes in escalating, de-escalating and stable self-administering flies.

Results: Our preliminary data suggests that, similar to mammals, individual variation in self-administration behavior occurs with consecutive training sessions. Approximately 30% of flies escalate self-administration whereas 50% of flies remain stable and 20% of flies decrease self-administration. This contrasts significantly with self-administration seen with appetitive food odors apple cider vinegar (15% of flies escalate) and 3% EtOH (0.08% escalate), and aversive odor benzaldehyde (.08% escalate). No significant differences were seen between male and female flies. Principle component analysis of subtle behavioral features provide a framework for defining motivation response in this operant assay.

Conclusions: Our data provides a behavioral groundwork to subsequently investigate variability in identified circuits contributing to drug and substance use disorders. Comparing the behavioral responses to natural aversive and appetitive stimuli to intoxicating doses of ethanol uniquely primes us to examine how natural and drug reward preference manifests in the nervous system of both male and female flies.

Keywords: Drosophila, Alcohol, Sex Differences, Machine Learning, Operant Behavior

Disclosure: Nothing to disclose.

T182. Prefrontal Cortical Functional Near Infrared Spectroscopy Measures During Working Memory Load Can

Detect and Classify Individuals as Impaired From Oral Delta 9-Tetrahydrocannabinol (THC)

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Background: In many states with legalized medical-use and adult-use cannabis, there is no legal limit of Δ9-tetrahydrocannabinol (THC) while operating a vehicle, as studies have shown that there is no evidence that a specific THC concentration in any body fluid is correlated with impairment for most individuals. Instead, intoxication or impairment must be demonstrated to trigger a legal violation of driving under the influence (DUI) of cannabis, which is typically accomplished by a police officer's observation of impaired driving behavior and a field sobriety test, which has not been scientifically validated, followed by analysis of urine for the presence of intoxicants or their metabolites. Thus, there is no empirical test of impairment from cannabis. We previously reported that prefrontal cortical (PFC) hemodynamic response during a working memory (n-back) task, detected with functional near infrared spectroscopy (fNIRS), is a biomarker of cannabis intoxication. Here, we sought to determine whether machine learning methods applied to fNIRS n-back task data could correctly classify individual participants as impaired from THC.

Methods: 176 adult regular cannabis users enrolled in a double-blind, placebo-controlled, cross-over study, and received up to 80mg of dronabinol, an FDA-approved synthetic THC and identical placebo in random order after overnight abstinence on two study visits one week apart. THC dose was individualized to produce intoxication, based on the degree of expected tolerance given self-reported average recreational cannabis dose, frequency, type, and self-reported intoxication and adverse effects, as well as sex, height, weight, BMI and baseline blood pressure. During each visit, participants completed the 100mm visual analogue Drug Effects Questionnaire (DEQ) scale, and had heart rate and blood pressure measured pre-dose and every 25 minutes post-dose to assess dronabinol effect(s) and 'high'. Participants completed a letter N-back working memory (WM) task (2-back and 0-back conditions) at baseline and at approximately 100 min (when peak dronabinol effects were expected) and 200 min post-THC administration. During the N-back task, participants underwent fNIRS scans using a continuous-wave NIRS device, with 8 sources and 7 detectors arrayed across the forehead, producing 20 channels covering PFC regions. Two raters (JG and AEE) assessed likelihood of impairment by considering post-drug self-rated intoxication, heart rate, blood pressure, and impairment assessments by blinded study staff and a Drug Recognition Expert. We extracted d' values from the N-Back task, and average HbO values from 5 regions of interest (ROIs; left and right ventral, left and right dorsal, and medial PFC), and computed difference scores (peak-minus pre-dose). We then examined correlations between change in d' and expert ratings of impairment. Machine learning methods were applied to the fNIRS data to develop participant level classification of impairment by optimizing Recurrent Neural Network (RNN) hyperparameters.

Results: There were significantly greater increases post THC than post placebo in DEQ ratings of drug effect and feeling high (mean peak ratings of 60.05 ± 30.35mm vs 10.08 ± 15mm and 62.05 ± 30mm vs 10.00 ± 15mm, respectively), in heart rate (mean increase at peak "high" was 16.97 ± 18.04bpm vs -0.01 ± 8.15bpm), and in oxygenated hemoglobin (HbO) concentration in the PFC during the 2-back task, most strongly in MPFC and bilateral DLPFC. This main effect of treatment on PFC activation was driven by participants who reported intoxication and were rated by investigators as likely impaired >75%, with few difference seen when raters determined that participants were <25% likely to be impaired post active THC. Notably, there was no significant correlation between THC dose and rater impairment rating, indicating that HbO increase was sensitive to impairment, not just presence of THC. For cognitive performance, there was a significant association between expert impairment rankings and n-back performance ($\beta. = -0.012$, $p = 0.0004$), such that higher impairment ratings post THC were associated with more impaired cognitive performance post study drug relative to baseline performance. Using a 5-fold cross-validation machine learning approach to evaluate the performance of the RNN, temporal feature maps were produced that exhibited high classification accuracies, with an average accuracy of 78%, and a maximum accuracy of 85%. In this model, specificity (true negative rate) was 85.3%, sensitivity (true positive rate) was 71.7%, and false positive rate was 14.8%.

Conclusions: We replicated in a larger sample our previous finding that HbO response during a working memory task changes significantly following THC administration, driven by intoxication measures such that this measure may be a useful biomarker of THC intoxication. We report an extension of this finding in that we achieve individual classification of impairment due to THC intoxication of up to 85% accuracy using standard ML techniques. We conclude that fNIRS is a promising tool for detection of impairment from cannabis intoxication, and may potentially be used to assess THC impairment with accuracy and specificity similar to the breathalyzer for impairment due to alcohol intoxication.

Keywords: Functional Near-Infrared Spectoscopy, Cannabis, N-back, Working Memory, Prefrontal Cortex

Disclosure: NIDA: Grant, Consultant (Self); HighLight-I: Patent (Self)

T183. How Does Race and Sex Impact the Relationship Between Childhood Trauma, Alcohol Consumption, and the Mediating Effect of Quality of Life?

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Background: Evidence suggests that racial/ethnic minorities and females are disproportionately impacted by alcohol-related problems. While several studies have found that non-Hispanic White individuals consume more alcohol and are younger at initiation of drinking, others have shown minority populations tend to report higher prevalence rates of alcohol use disorder (AUD) and negative social and health effects at lower levels of heavy drinking. Gender disparities work shows that men drink more frequently and at higher rates than women and are more likely to transition to an AUD. Numerous studies have evidenced the relationship between adverse childhood experiences (ACEs) and increased risk for negative health outcomes, including AUD. Several studies have shown that racial/ethnic minorities and females have a greater risk of ACEs exposure. In addition, research has shown that racial/ethnic minorities report greater prevalence of ACE. Despite the vast amount of research examining the relationship between ACEs and alcohol-related problems, the relationship is less clear when examining the combined effects of race and sex. This study aimed to examine the relationship between ACE, sex and race on drinking outcomes, and the potential mediating role of quality of life on these relationships.

Methods: This study included 1135 male and female participants stratified into Nonproblematic Drinkers, ND ($N = 513$) and

Problematic Drinkers, PD ($N = 622$). We used the Structured Clinical Interview for Diagnostic and Statistical Manual of mental disorders (both DSM-IV and DSM-5) to assess alcohol problems. ND included individuals with no history of alcohol problems while PD included those with a past and/or current diagnosis of alcohol abuse, alcohol dependence or AUD. Participants completed assessments of ACE (Childhood Trauma Questionnaire, CTQ), and quality of life (World Health Organization Quality of Life scale, QOL). The Environmental subscale of QOL (EQOL) which has facets such as financial resources, physical safety, and health care availability, was included in the analyses. Drinking behaviors were assessed using the Alcohol Use Disorder Identification Test (AUDIT) and 90-DayTimeline Followback (TLFB) using the measures of heavy drinking days (HDD) and drinks per drinking day (DPD).

Results: Both the ND and PD samples saw significant main effects of race, sex and/or interaction effects between race and sex on drinking measures. In the ND sample there were significant main effects of sex on AUDIT ($P = 0.007$), DPD ($P \leq 0.001$), HDD ($P = 0.004$) where males scored significantly higher than females. There was also a significant main effect of race with White participants scoring higher than Black participants on the AUDIT ($P \leq 0.001$). In addition, there was a race*sex interaction effect on HDD ($P = 0.003$; Black females < Black males).

In the PD sample, there was a significant main effect of sex on AUDIT-C ($P = 0.026$) with males scoring higher than females. There were significant main effects of race for HDD ($P = 0.017$) and AUDIT ($P = 0.004$). Black participants scored higher on HDD, while White participants scored higher on the AUDIT. There was also a significant race*sex interaction effect for AUDIT ($P = 0.003$; Black females < White females).

As expected, the PD sample endorsed ACE more so than the ND sample. In the ND sample, Black participants reported higher scores than White participants for CTQ total ($P = 0.001$) and several subscales (all p's≤0.03). Sexual abuse was the single main effect of sex where females scored higher than males ($p = 0.021$). There was also a significant race*sex interaction effect on emotional neglect ($P = 0.032$; Black females > White females).

For the PD sample, Black participants also reported higher scores than White participants for CTQ total ($p = 0.023$) and several subscales (all p's≤0.023). Females reported higher scores than males for CTQ total ($p = 0.025$) and several of the subscales (all p's≤0.037). There were no significant race*sex interaction effects on any of the ACEs measures.

A moderated mediation analysis was conducted to examine the effect of race and sex on the relationship between CTQ total score and AUDIT total score with EQOL as a mediator. EQOL mediated the relationship between CTQ total score and AUDIT total ($R2 = 0.31$, $P<0.0001$). CTQ ($P=0.004$), race ($P = 0.045$), sex ($P = 0.007$), and the interaction of race*sex ($P = 0.041$) significantly predicted EQOL scores. AUDIT scores were predicted by EQOL ($P = 0.029$) while CTQ*race showed a trend-level effect ($P = 0.052$). The indirect effect of CTQ on AUDIT score was significant for both Black and White participants with a stronger effect size for Black participants. The conditional direct effect of CTQ on AUDIT score was significant for White participants only and had a positive relationship. This model covaried for problematic drinking status ($P<0.001$) and sex (N.S.) as well as age, household income, and years of education (all p's <0.05).

Conclusions: In conclusion, both race and sex significantly moderate the mediating effects of EQOL on the relationship between ACE and drinking measures, with conditional direct effects showing significance only in White participants. Future analyses will explore other environmental and personality determinants of the relationship of ACE and alcohol behaviors across race and sex. By understanding differential risk across groups, preventive and intervention strategies will be better informed.

Keywords: Childhood Trauma, Alcohol Use Disorder, Quality of Life, Health Disparities

Disclosure: Nothing to disclose.

T184. Nuclear Factor Kappa B Signaling Within the Rat Nucleus Accumbens Core Modulates Cue-Motivated Reward-Seeking Behavior

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Background: Chronic drug self-administration and withdrawal are associated with distinct neuroimmune adaptations, such as increased neuroinflammation, that may increase drug craving and relapse vulnerability in humans. Neuroinflammation is associated with nuclear factor kappa B (NF-κB) signaling, which subsequently modulates the expression of many addiction-related genes. Cocaine exposure upregulates the expression of p65 subunit of NF-κB, suggesting increased activation of NF-κB signaling. Moreover, inhibition of upstream IκB kinase (IKK) signaling within the nucleus accumbens (NAc) decreases cocaine-induced conditioned place preference, and we have shown that inhibition of IKK signaling within the NAc core of rats decreases cue-induced reinstatement of extinguished nicotine seeking. Nevertheless, no studies to date have examined whether direct knockdown of p65 within the NAc core decreases cue-motivated cocaine seeking following a period of forced abstinence, which is a model of incentive motivation for cocaine that better recapitulates the human condition. As well, no studies to date have examined whether these effects of NAc core NF-κB signaling are specific to drugs of abuse. Here, we examined whether lentiviral knockdown of p65 within the NAc core of rats would decrease cue reactivity to cocaine- and sucrose-associated cues following a period of forced abstinence.

Methods: 12 Sprague-Dawley rats that self-administered cocaine were surgically implanted with a jugular vein catheter and intra-NAc core guide cannulas. Rats self-administering sucrose received only intra-NAc core guide cannulas. Animals were food restricted and were trained to self-administer cocaine (0.75 mg/kg, i.v.) or sucrose (45 mg/pellet, p.o.) for 2 h/d for a minimum of 12 days. Initially, cocaine or sucrose was available on a FR1 schedule, where an active lever press triggered a light cue above the active lever and a tone cue (500 Hz), followed by delivery of either cocaine (over the 6 s cue duration) or sucrose. This was followed by a 20-s timeout period, signaled by the house light, where no reinforcers or cues were available. Within each session, the schedule progressed to a variable ratio (VR) 2, 3, and 5 sequentially after a rat achieved 5 reinforcers within any given hour. Between sessions, the beginning schedule (FR1, VR2, VR3, or VR5) increased if the animal ended its three previous sessions on a VR5. Following self-administration, animals received intra-NAc core microinfusions of a lentivirus (LV) that expressed a p65 shRNA and the fluorescent reporter turboGFP (LV-p65shRNA-tGFP), or control LV (LV-tGFP) on day 1 of abstinence. Rats remained in abstinence for 21 days prior to a 1-hr cue reactivity test, where active lever presses resulted in delivery of reinforcer-paired discrete cues but no reinforcer. Immediately after cue reactivity testing, rats were sacrificed for tissue collection to assess viral transgene expression within the NAc core. All procedures were approved by the Arizona State University Institutional Animal Care and Use Committee and adhered to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Results: Rats treated with LV-p65shRNA-tGFP and LV-tGFP earned a similar number of total cocaine infusions or sucrose

pellets earned during self-administration. Rats that self-administered cocaine and were treated with LV-p65shRNA-tGFP ($n = 3$) did not significantly differ in active lever presses relative to those treated with LV-tGFP ($n = 3$) in the cue reactivity test. However, rats that self-administered sucrose and were treated with LV-p65shRNA-tGFP ($n = 3$) showed a trend towards decreased active lever presses compared to those treated with LV-tGFP ($n = 3$, $t(4) = 2.172$, $p < 0.10$). Immunohistochemistry analyses verified tGFP expression within the NAc core of LV-treated rats. Additional subjects are currently in training to increase statistical power.

Conclusions: Our preliminary results suggest that NF-κB signaling modulates cue-motivated sucrose-seeking following a period of abstinence, when incentive motivation is thought to progressively increase over time. Therefore, our preliminary results suggest that the role of NF-κB in cue-motivated reward seeking may not be limited to drugs of abuse and may generalize to natural reinforcers as well. Importantly, our studies highlight the need to further investigate NF-κB signaling within the mesolimbic reward system and determine whether the environmental context in which cues are facilitating reward-seeking behavior plays a deciding role in the function of NF-κB in driving such behavior. Studies are ongoing to increase the sample size and to test female rats to examine potential sex differences in our observed effects. Our findings increase understanding of how immune signaling regulates conditioned reward-seeking behavior.

Keywords: Nuclear Factor Kappa B, Neuroimmune Mechanisms, Cocaine Self-Administration, Cue Reactivity

Disclosure: Nothing to disclose.

T185. Metadoxine Reduces Alcohol Consumption in a Double-Blind, Placebo-Controlled, Pilot Study in Patients With Alcohol Use Disorder

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Background: Alcohol use disorder (AUD) is a leading cause of preventable death in the United States and globally, with over 88,000 deaths related to alcohol use in the US alone with approximately one-quarter of these related to alcoholic liver disease. Thus, there is a critical need to develop additional pharmacotherapies for patients with co-morbid alcohol use disorder (AUD), including those with alcohol liver disease (ALD). A medication that is safe for the liver, reduces the damaging effects of alcohol on the liver, and is able to reduce alcohol consumption would be an ideal medication, especially for patients with comorbid AUD and ALD.

Metadoxine (MTDX) has been proposed as a useful treatment for both AUD and ALD. Metadoxine treatment increases the clearance of alcohol and acetaldehyde, reducing the damaging effect of free radicals and restoring both cellular adenosine triphosphate (ATP) and glutathione levels. Metadoxine is approved in some European countries for acute and chronic alcohol intoxication. In addition, several studies have shown that MTDX is an effective treatment for ALD. Moreover, preliminary evidence indicates that MTDX reduces alcohol consumption in AUD patients. However, these studies either were not blinded, not prospective, or of short duration. If the role of MTDX in reducing alcohol consumption is confirmed, then MTDX would provide a truly innovative pharmacotherapy option for AUD, given the potential to be used for AUD patients with ALD.

The purpose of this study is to determine the efficacy of MTDX in improving drinking outcomes and markers of liver disease in AUD patients using a double-blind, placebo-controlled design.

Methods: This 4-month, randomized, double-blind, placebo-controlled pilot study was conducted at the Brown University Center for Alcohol and Addiction Studies from July 9, 2012 to April 2, 2015. Eligible patients met carried a diagnosis of DSM-IV alcohol dependence. Patients (10 male and 4 female) were randomized to receive either MTDX 500mg TID or placebo for 12 weeks and daily quantity of drinking was assessed using the Timeline Follow-back Interview. All analyses were of the intention-to-treat type. Continuous drinking outcomes were measured by month. The primary outcome was percent days abstinent and other secondary outcomes included drinks per drinking day (DPDD), percent heavy drinking days (PHDD) and three categorical responder outcomes. Mixed models controlling for baseline were used to analyze PDA, DPDD, and PHDD. Chi-square analyses examined group differences in binary responder outcomes which included no heavy drinking days (NHDD) during the 4-month treatment period, NHDD in the last month, and 50% heavy drinking reduction from baseline relative to the last month of treatment. Labs to assess liver function were collected monthly.

Results: Of the 36 patients assessed for eligibility, 14 were randomized with 7 in each arm. Four were women (29%), 6 were non-white (43%), and the mean (SD) age was 52.3 (9.18) years.

We found a significant treatment effect in PHDD (LSMD = −33.95%, 95% CI -66.83 to -1.15, $F = 5.24$, $p = 0.04$), a significant treatment by time effect in DPDD ($F = 8.93$, $p = 0.01$), but no group differences in PDA ($F = 0.88$, $P = 0.37$) or DPDD ($F = 1.97$, $P = 0.19$).

We found no group differences in NHDD when considering either the 4-month period or the last month of treatment. For 50% heavy drinking reduction from baseline, while there was no significant difference ($p = 0.24$, OR = 4.50, CI: 0.34–60.15) between MTX (42.86%) and placebo (14.29%), the trend suggests patients in MTX group had benefit over placebo.

There were no observed differences in AST and ALT in this small sample.

Conclusions: In this small preliminary study, metadoxine demonstrated promising results for continuous measures of drinking including PHDD and DPDD. These results merit further study of metadoxine for the treatment of Alcohol Use Disorder. Given the known relationship between the quantity of alcohol consumption and liver disease, future studies should be powered to examine improvements in liver enzymes in addition to improvements in drinking outcomes.

Keywords: Alcohol Use Disorder - Treatment, Alcoholic Liver Disease, Novel Therapeutics

Disclosure: Nothing to disclose.

T186. Characterization of Alpha-1 Receptors in Individuals With Alcohol Use Disorder

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Background: The role of norepinephrine (NE) in the development of alcohol use disorder (AUD) has been evaluated over the past several decades. In order to better characterize the role of alpha-1 receptors in individuals with AUD, we tested the hypothesis that central functional activity of alpha-1 receptors decreases with age.

Methods: In Study 1, we used the GTEx dataset available via the Human Protein Atlas to analyze the relationship between age and alpha-1A, B, and D receptor expression (pTPM) in nine regions (amygdala, anterior cingulate, caudate, hippocampus, hypothalamus, nucleus accumbens, putamen, frontal cortex, and general

cortex) of postmortem brain tissue ($N = 100$-160). Then, in Study 2, to selectively include the AUD clinical diagnosis, we measured alpha-1B receptor mRNA extracted in five brain regions (amygdala, hippocampus, ventral tegmental area, nucleus accumbens and prefrontal cortex) in human postmortem brain available from male subjects diagnosed with AUD and compared to healthy controls ($N = 27$). Finally, in Study 3, we conducted a secondary analysis of a 10-weeks, randomized, double-blind placebo-controlled clinical trial (RCT) using doxazosin, an alpha-1A, B, D receptor antagonist, to evaluate if age was a moderator in alcohol drinking reduction in treatment seekers individuals with AUD ($N = 41$).

Results: Study 1 revealed a significant negative correlation of age with alpha-1A receptor expression in the amygdala, anterior cingulate, caudate, hippocampus, hypothalamus, nucleus accumbens, and putamen ($r = -0.16$ to -0.35, p's < 0.04–0.0001). There was a negative correlation of age with alpha-1B expression in the amygdala, anterior cingulate, hippocampus, hypothalamus, and general cortex ($r = -0.204$ to -0.358, p's < 0.05 – 0.0001). Age was negatively correlated with alpha-1D expression in the anterior cingulate, hippocampus, hypothalamus, nucleus accumbens, frontal cortex, and general cortex ($r = -0.237$ to -0.443, p's < 0.01–0.0001). In Study 2, we found no significant difference in alpha-1B expression in any brain region between individuals with AUD and healthy controls (p's>0.05). In Study 3, we found a significant age x doxazosin interaction for drinks per week (DPW) ($F1,36 = 4.869$, $p < 0.05$) and a trend towards significance for heavy drinking days (HDD) ($F1,36 = 3.322$, $p = 0.077$). Post hoc analysis showed a significant effect of doxazosin, in reducing DPW ($t34 = -2.34$, $p < 0.05$) and HDD ($t34 = -3.138$, $p < 0.01$) in younger individuals.

Conclusions: These findings support a relationship between age and central alpha-1 receptor expression in AUD. This work further provides justification for a personalized medicine approach for treating AUD.

Keywords: Alpha-Adrenergic, Alcohol Use Disorder, MRI, Aging

Disclosure: Nothing to disclose.

T187. Sex Differences in I.V. Oxycodone Self-Administration and Cue-Induced Reinstatement of Oxycodone Seeking in Rats: Role of Estrous Cycle

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Background: Prescription opioid abuse has emerged as a major public health crisis in the United States, resulting in alarming rates of overdose-related deaths and significant economic burden. Oxycodone is among the most frequently prescribed opioid analgesics and its misuse has contributed to the current opioid epidemic. While sex differences have been reported for the abuse-related effects of opioids in both humans and experimental animals, only a small number of studies to date have examined sex differences specifically with respect to oxycodone. In the present studies, we sought to compare the reinforcing effects of oxycodone and the magnitude of cue-induced oxycodone-seeking behavior between male and female rats using i.v. oxycodone self-administration and reinstatement procedures. We also assessed whether these measures varied in females as a function of estrous cycle.

Methods: For dose-response studies, adult male ($n = 4$) and female ($n = 4$) Long-Evans rats were first trained to self-administer 0.03 mg/kg/infusion oxycodone according to a fixed-ratio 1 schedule of reinforcement in daily 2-hr sessions (5-6 days per week). Stable response rates (<30% variability in active-lever responses and <20% variability in reinforcers earned across 3 consecutive sessions) were then assessed when 0.03, 0.01, or 0.003 mg/kg/infusion were available, with doses presented in descending order. A separate group of adult male ($n = 7$) and female ($n = 7$) Long-Evans rats were trained to self-administer 0.03 mg/kg/infusion oxycodone for 8 days, followed by 0.01 mg/kg/infusion oxycodone for 10 days. Responding was then extinguished in daily 2-hr sessions during which active-lever responses had no scheduled consequences, and subsequently reinstated by reintroducing a response-contingent cue light that had previously been paired with oxycodone infusions. Vaginal smears were collected daily from female subjects for histological confirmation of estrous cycle phase (proestrus, estrus, metestrus, diestrus).

Results: In the dose-response experiment, varying the unit dose of oxycodone produced an inverted U-shape function, with 0.01 mg/kg/infusion at the peak of the curve in both sexes. Oxycodone functioned as a more effective reinforcer in females than males, maintaining higher rates of responding and resulting in more infusions earned, particularly at the two lower doses tested (Main Effect of sex, $p < 0.05$). In the reinstatement experiment, females again exhibited higher rates of responding than males at both doses of oxycodone. In females, rates of responding at either dose of oxycodone were significantly higher during metestrus/diestrus as compared to proestrus/estrus (Main Effect of phase, $p < 0.05$). Finally, cue-induced reinstatement of previously-extinguished oxycodone-maintained responding was greater in females as compared to males ($p < 0.05$), although there was no clear effect of estrous cycle phase on this measure in females.

Conclusions: Our results indicate that i.v. oxycodone exerts greater reinforcing effects in female rats as compared to males, in agreement with previous reports. Females also exhibited a more robust drug-seeking response following re-exposure to oxycodone-associated discrete cues than males, suggesting that sex differences are applicable not only to oxycodone taking, but also to oxycodone seeking. We also reveal for the first time that the reinforcing effects of i.v. oxycodone are modulated by estrous cycle phase, an effect that is likely mediated by fluctuations in ovarian hormones. Taken together, our results confirm and extend previous work suggesting that females may be at greater risk than males for developing opioid use disorder and/or for suffering a relapse event, although the magnitude of these risks may vary in different phases of the menstrual cycle.

Keywords: Oxycodone, Sex Differences, Cue Reinstatement, Estrous, Intravenous Drug Self-Administration

Disclosure: Nothing to disclose.

T188. Differential Importance of Nucleus Accumbens Signaling for Female and Male Binge Alcohol Drinking in Mice

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Background: Alcohol use disorder extracts substantial social and economic costs, and in recent years the rate of problem drinking in females has nearly matched that in males. Thus, it is critically important to understand differences in signaling systems that drive alcohol intake across the sexes. Orexin acting through orexin-1 receptor (Ox1R) can strongly contribute to motivated behavior, and our previous work identified Ox1R signaling within nucleus accumbens shell (Shell) as a critical mediator of binge alcohol intake in higher-drinking male mice.

Methods: Intracranial (in nucleus accumbens Shell) and systemic administration of orexin-1-receptor blocker and intra-Shell calcium-permeable AMPA receptor blocker were tested for effects on limited access 2-bottle choice alcohol drinking in male and female mice. Some studies examined quinine-resistant

alcohol intake to model compulsion-like drinking. Controls examined saccharin intake.

Results: Here, we demonstrate that Ox1R inhibition within the Shell (with SB-334867) had no effect on female alcohol drinking ($p = 0.8934$), unlike what we observed for males. In contrast, inhibition of the calcium-permeable AMPA receptor with NASPM in the Shell significantly and strongly reduced alcohol drinking in both females and males (female: 62.8 ± 8.3% decrease in intake, $p < 0.0001$; male: 42.5 ± 8.8% decrease in intake, $p = 0.0023$). This NASPM effect was specific for alcohol, since Shell infusion of NASPM did not reduce saccharin intake in either sex. In addition, systemic Ox1R inhibition did significantly reduce compulsion-like alcohol intake in females, similar to what we reported for males, indicating that Ox1Rs can act within females to drive some aspects of pathological alcohol consumption. Similarly, higher doses of Ox1R inhibition (which might have more off-target effects) reduced binge drinking in both sexes.

Conclusions: Our results together suggest that the Shell was a critical regulator of binge alcohol drinking in both sexes, but Shell AMPA receptors supported intake in both sexes while Shell Ox1Rs drove alcohol drinking only in males. Our findings provide important new information about sex-specific and -general mechanisms that promote binge alcohol drinking, which may help shape our understanding of the drive to drink in each sex and possible therapeutic interventions.

Keywords: Binge Drinking, Orexin, AMPA Receptors, Alcohol, Compulsive Behavior

Disclosure: Nothing to disclose.

T189. Differential Control of Kappa Opioid Receptors on Monoaminergic Systems Across the Rostro-Caudal Axis in Nucleus Accumbens Shell

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Background: The nucleus accumbens (NAc) shell is a heterogenous area that receives dopaminergic input from the ventral tegmental area and serotonergic input from the dorsal raphe nucleus. Both dopamine and serotonin are involved in regulating addictive and affective behaviors. The dynorphin/kappa opioid receptor (KOR) system has a powerful inhibitory control over the monoaminergic neurotransmission in the NAc shell and shapes behavioral outcomes. Recent studies have shown a regional difference in KOR mediated behavioral outcomes; particularly, KOR activation in the rostral NAc shell promotes hedonic behaviors. On the contrary, KOR activation in the caudal NAc shell profoundly reduces the hedonic behaviors. In the current study we first establish regional differences in dopaminergic and serotonergic inputs along the rostro-caudal axis. Then we determine the control of KORs over these monoaminergic projections.

Methods: We measured dopamine and serotonin excitability in rostral and caudal NAc shell using ex vivo fast scan cyclic voltammetry (FSCV) in male and female rats. Specifically, we used tonic (single pulse and 5 pulses at 5 Hz) and phasic (2 pulse and 5 pulses at 10, 20, 100 Hz) stimulation parameters and measured dopamine and serotonin release in the two subregions of NAc shell. In addition, we measured the effect of KOR activation using the selective KOR agonist, U50488 (0.01 – 1.0 uM), on dopamine and serotonin transmission in rostral and caudal NAc shell. For behavioral experiments, rats were subject to light-dark box and novel environment assays in order to examine avoidance/approach behavior and rearing activity, respectively.

Results: Voltammetric measurements of dopamine following phasic stimulation revealed that the increasing stimulation frequencies resulted in significantly greater dopamine release in both rostral and caudal NAc shell; however, the elevation in dopamine release was enhanced in caudal compared to rostral shell. While increasing stimulating frequencies resulted in augmented serotonin release in both rostral and caudal NAc shell, the increase was comparable in the two regions. Interestingly, KOR-activation mediated inhibition of dopamine release was significantly greater in caudal, compared to rostral shell. In contrast, KOR-activation mediated inhibition of serotonin was significantly greater in rostral compared to caudal shell. Our behavioral data show that KOR-activation in caudal NAc shell stimulated novelty-induced rearing behavior and enhanced avoidance behavior. In contrast, activation of KORs in the rostral NAc shell augmented approach behavior.

Conclusions: Together, these data indicate that dopamine projections in the rostral and caudal NAc shell are possibly distinct, whereas the serotonin projections are likely comparable across the rostro-caudal axis. Furthermore, KOR system control over dopamine is regionally opposite to its control over serotonin. Lastly, the greater KOR-mediated inhibition of dopamine in caudal shell likely drives anhedonia whereas KOR-mediated inhibition of serotonin drives hedonic responses. Taken together, these results indicate that there is heterogeneity across the rostro-caudal axis of the NAc shell in the effects of KOR stimulation on affective behaviors, and they suggest that this might be due to differences in KOR control over dopamine and serotonin release.

Keywords: Dopamine, Serotonin, Kappa Opioid Receptors, Fast Scan Cyclic Voltammetry

Disclosure: Nothing to disclose.

T190. Using the Novel Synthetic Neurosteroid SGE-516 to Modulate the Escalation of Binge Drinking and its Consequences in Male and Female Mice

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Background: Post-traumatic stress disorder (PTSD) is one of the most prevalent co-occurring psychiatric pathologies among individuals with alcohol use disorder (AUD). Although comorbidity worsens the symptoms of both disorders, and worsens their prognosis following treatment, no approved compound has demonstrated efficacy to treat AUD comorbid with PTSD. GABAergic neuroactive steroids are significantly altered by chronic alcohol and play a role in the stress and arousal systems degraded in PTSD. In particular, dampened plasma levels of allopregnanolone are found in individuals with alcohol dependence or undergoing alcohol withdrawal and in men and women with PTSD. Indeed, a long history of work support allopregnanolone as playing an integral role in the development or progression of AUD. However, allopregnanolone shows sex-specific effects on alcohol drinking in animal models, and previous clinical trials using a synthetic allopregnanolone analogues suggest low bioavailability in humans following oral administration. The goal of our present work was to establish whether a novel synthetic neurosteroid GABA(A) receptor positive allosteric modulator, SGE-516, could successfully disrupt the escalation of binge drinking or block the consequences of chronic alcohol exposure in both male and female mice.

Methods: C57BL/6J mice received 3hr limited access to alcohol (20%, v/v) in a manner that induces escalated binge alcohol intake. On the 7th day of binge drinking, the synthetic neurosteroid SGE-516 (450mg/kg; chow) was introduced in place of regular chow and binge drinking behavior for the next 7 days was recorded. After a 14 day withdrawal period, behavior in the elevated plus maze was assessed in mice with a history of ethanol drinking with or without SGE-516 treatment, and compared to

similarly treated water drinking controls. Behaviors were coded by experimenters blinded to treatment groups and all procedures were approved by Wesleyan University's Institutional Animal Care and Use Committee. Data were analyzed for males and females were analyzed and presented separately, using repeated-measures ANOVA and *t*-tests where appropriate. Sample sizes for data presented below are: Males: $n = 9$ - 11 mice/chow group/fluid group; Females: $n = 4$–6 mice/chow group/fluid group.

Results: For males ($n = 11$ control, $n = 9$ treated), a two-way ANOVA on daily intake across the 2 weeks of access failed to reach significance for a treatment-group by day effect [$F(13, 234) = 1.098$, $p = 0.3$)-as males usually do not escalate their intake during this paradigm. However during the treatment week, intakes were marginally lower for SGE-516 treated males when compared to the standard chow group ($t18 = 1.82$, $p = 0.08$). Males with a history of binge drinking did not show a significant effect of alcohol exposure on behavior in the elevated plus maze. However, there remained a significant group effect [$F(2,13) = 4.19$, $p < 0.05$], as males with a history of binge drinking and SGE-516 treatment spent a greater percent of time in the open arms than water-only controls ($p = 0.02$).

Preliminary evidence in females ($n = 4$–6 per treatment group) suggests that SGE-516 modulated binge drinking, as a two-way rmANOVA found a marginal interaction between treatment-group and day [$F(13, 234) = 1.098$, $p = 0.08$). Intakes were averaged and compared across two weekly bins to follow our previous definitions of "escalation" in this paradigm. Untreated females reliably escalated their binge consumption of alcohol, showing greater intake during week two than week one, whereas SGE-516 females failed to show a change from their initiation intakes. Relatedly, average intake during the drug chow week was marginally different between SGE-516 treated and standard chow groups ($t8 = 2.18$, $p = 0.06$), with SGE-516 treated mice consuming 25% less alcohol than controls. For withdrawal behavior two weeks after the cessation of both alcohol and SGE-516 treatment, there was a main effect of group [$F(2, 13) = 4.249$, $p < 0.05$) as females with a history of binge drinking spent a greater percent of time in the open arms of the plus maze ($p < 0.05$), while SGE-516 treated females with a history of binge drinking showed behavior similar to water-only controls ($p = 0.99$).

Though there was no difference in quantity of drug chow consumed across sexes (Males consumed 4.83 g/day; Females consumed 4.43 g/day), data collection and analysis quantifying pharmacokinetics remain to be completed.

Conclusions: These findings suggest that synthetic neurosteroids may indeed be a successful treatment strategy to temper binge drinking and is a successful treatment strategy to block the expression of withdrawal behaviors associated with chronic alcohol exposure. Future work will establish whether this compound can block stress-escalated drinking in our mouse model for comorbid PSTD/AUD.

Keywords: Allopregnanolone, Neurosteroids, Alcohol Use Disorder - Treatment, SGE-516, GABA

Disclosure: Nothing to disclose.

T191. SK609, a Novel Dopamine D3 Receptor Agonist and Norepinephrine Transporter Blocker With Pro-Cognitive Actions, Does Not Induce Psychostimulant-Like Increases in Risky Choice During Probabilistic Discounting

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Background: Cognitive and reward-related processes are modulated by catecholamine circuits, such as norepinephrine (NE) and dopamine (DA) input to the prefrontal cortex (PFC). Psychostimulants block reuptake and elevate extracellular concentrations of both NE and DA, and are common pharmacological strategies used to improve PFC-dependent behavioral dysfunction associated with neuropsychiatric disorders like attention deficit hyperactivity disorder (ADHD). However, this approach can be problematic given the side effect liability and abuse potential of psychostimulants. SK609 is a novel NE reuptake blocker that selectively activates DA D3 receptors without affinity for the DA transporter. SK609 has been shown to improve sustained attention similar to the ADHD-approved psychostimulant methylphenidate (MPH), but not produce MPH-like increases in spontaneous locomotor activity associated with DA transporter activity. These findings suggest SK609 may help ameliorate neurocognitive impairments without psychostimulant-like side effects. The probabilistic discounting task (PDT) is a well-established preclinical assay for risk/reward decision making that resembles risky gambling behavior in humans. Psychostimulant drugs such as amphetamine (AMPH) increase risky choice behavior on this task.

Methods: The present set of experiments evaluated the pro-cognitive drugs, AMPH, MPH, and SK609, for their potential to produce psychostimulant-like increases in risky choice behavior using the PDT.

Results: In well-trained male rats, AMPH and MPH increased risky choice at doses known to improve other forms of cognition, with this effect being driven by a reduction in sensitivity to non-rewarded risky choices (i.e. lose-shift behavior). In contrast, SK609 did not affect overall risky choice, but tended to increase win-stay and lose-shift behavior, suggesting that this compound enhances the influence that recently rewarded and non-rewarded actions exert over subsequent choice.

Conclusions: These data show SK609 has ability to produce favorable effects on behavioral outcomes in other domains of cognition mediated by the PFC, without psychostimulant-like side effect liability assessed with the PDT. These data also highlight the roles of NE transporter blockade and selective D3 activation in pro-cognitive action. The absence of DA transporter blockade and non-selective dopaminergic elevation are beneficial properties of SK609 that differentiates it from the traditional pro-cognitive psychostimulants.

Keywords: Reinforcement-Based Decision-Making, Reward-Based Decision-Making, D3 receptor, Behavioral Pharmacology, Operant Behavior

Disclosure: Nothing to disclose.

T192. Exposure to Chronic Witness Defeat Stress Elicits Stress-Induced Increases in Fentanyl Consumption in Male and Female C57BL/6 Mice

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Background: The opioid epidemic is an urgent, ongoing public health crisis. Approximately 100 Americans die from an opioid-related drug overdose every day. Unfortunately, potent synthetic opioids, such as fentanyl, have accelerated rising opioid-related drug overdose. As a result, there is a critical need to investigate factors that may facilitate the initiation and development of opioid use disorder. One such risk factor, exposure to social stress, has been shown to increase the likelihood of escalated cocaine, alcohol, and amphetamine consumption in preclinical research. However, Chronic Social Defeat Stress (CSDS), a common paradigm used to achieve social stress, often produces both social and physical stress. Given that opioids possess inherent

analgesic properties, it is important to delineate between analgesic and rewarding effects when examining the potential stress-sensitization of opioid consumption. Chronic Witness Defeat Stress (CWDS), a recently validated paradigm that only produces social stress, provides an opportunity to examine stress-sensitized opioid consumption. Thus, the overall goal of the current study was to evaluate stress-induced changes in fentanyl consumption using CWDS and escalating fentanyl two-bottle choice paradigms.

Methods: Male and female C57BL/6 mice were subjected to 10 days of CWDS, during which subjects indirectly experienced the direct social defeat of a male C57BL/6 intruder mouse by a male CD1 aggressor. CWDS was followed by a social interaction test to determine susceptible (avoids behavioral interaction with a novel social target) and resilient (approaches behavioral interaction with a novel social target) behavioral groups. Once susceptible and resilient behavioral phenotypes were established, mice completed a 15-day escalating fentanyl two-bottle choice paradigm that comprised of three distinct periods of forced fentanyl access, each characterized by a higher dose of fentanyl (i.e. 5, 10, and 15 µg/mL). Each period of forced fentanyl access lasted four days and was followed by a choice day of voluntary fentanyl consumption wherein mice were allowed access to both fentanyl and water. Mice were provided a 10 µg/mL solution of fentanyl on the first-choice day and a 15 µg/mL solution on the second and third choice days. A second social interaction test was carried out three days after the completion of the fentanyl two-bottle choice paradigm to assess susceptible and resilient behavioral phenotypes after fentanyl exposure.

Results: Our data indicate that exposure to CWDS produces stress-induced increases in fentanyl consumption. Specifically, both resilient and susceptible male mice consumed more fentanyl during all three forced access periods compared to their control (no CWDS) counterparts. In contrast, susceptible female mice voluntarily consumed more fentanyl compared to their resilient counterparts and demonstrated higher fentanyl preferences compared to female control and resilient groups during the third-choice day. Male mice subjected to CSDS demonstrated similar patterns of fentanyl consumption. In particular, susceptible male mice preferred and consumed more fentanyl compared to their resilient counterparts during the second period of forced and voluntary access to fentanyl. Thus, both CWDS and CSDS paradigms can yield stress-induced changes in fentanyl consumption. Furthermore, both resilient male and female mice displayed a decrease in social interaction after completion of the fentanyl two-bottle choice paradigm, suggesting that fentanyl exposure itself can negatively impact social behavior.

Conclusions: Taken together, findings from the current study suggest that exposure to social stress can increase vulnerability to opioid misuse in both susceptible and resilient populations. Future work aims to elucidate changes in gene expression in fentanyl drinking susceptible and resilient mice and evaluate whether aversive emotional states can increase the motivational properties of opioids using a self-administration paradigm.

Keywords: Opioid Abuse, Social Defeat Stress, Fentanyl

Disclosure: Nothing to disclose.

T193. Activation of G Protein-Coupled Estradiol Receptor 1 in the Dorsolateral Striatum Attenuates Preference for Cocaine and Saccharin Rewards in Male but not Female Rats

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Background: There are sex differences in susceptibility to addiction where females appear to be more vulnerable than males. Extensive research has shown that the gonadal hormone, estradiol (E2), enhances the rewarding properties of cocaine for females and increases their motivation to engage in drug-seeking behaviors. These studies, however, have largely focused on the role of classical receptors, ERα and ERβ which has led to a gap in our understanding of the role of the third E2 receptor, GPER1. Additionally, while E2 is a prominent hormone in males, as well as females, the role of E2 in male drug seeking has not been extensively investigated. Therefore, the aim of the current study was to identify whether activation or inhibition of the E2 receptor, GPER1, in the dorsolateral striatum (DLS) alters preference for cocaine or saccharin in female and male rats.

Methods: A total of 46 male and 30 female rats were included in our first study which identified how ER manipulation alters cocaine conditioned place preference (CPP). Rats underwent surgery for the implantation of bi-lateral guide cannula into the DLS. Stylets were inserted into the guide cannula and delivered continuous treatment of either ICI (ERα/ERβ antagonist; GPER1 agonist), G1 (GPER1 agonist), G15 (antagonist) or Cholesterol (vehicle). Time spent in the drug-paired chamber before and after conditioning determined whether each animal developed a cocaine CPP.

For our second study, 12 male and 12 female rats were used to identify whether GPER1 activation, using G1, alters preference for 0.1% saccharin verse plain H2O. As described above, rats underwent surgery for the implantation of bi-lateral guide cannula into the DLS where treatment stylets were subsequently administered. In this study, preference for saccharin was determined using as two-bottle choice paradigm where each animal had access to two bottles filled with either 0.1% saccharin or plain H2O. The amount of liquid consumed from either of the bottles was used to identify whether each animal developed a preference for saccharin.

All animal care and experimental procedures were carried out in accordance with the National Institutes of Health guidelines on laboratory animal use and care and were approved by University of Michigan Institutional Animal Care and Use Committee.

Results: We found that males treated with ICI did not form a preference for the drug-paired chamber (i.e., no CPP) however, CHOL treated males did form a CPP ($p = 0.0004$). To differentiate whether the effects of ICI were due to inhibition of ERα/ERβ or activation of GPER1, we administered G1, a selective GPER1 agonist. Again, we found that males treated with G1 ($p = 0.3804$) did not form a CPP for cocaine, but CHOL ($p = 0.0001$) treated males did. In order to determine if GPER1 manipulation in the DLS could bidirectionally modulate cocaine CPP, we also administered G15, a selective GPER1 antagonist. We found that males treated with G15 into the DLS formed a CPP ($p = 0.0406$) for a sub threshold dose of 5mg/kg cocaine while CHOL treated males did not. These results suggest that activation of GPER1 in the DLS is sufficient to attenuate preference for 10mg/kg cocaine in males and inhibition of GPER1 is sufficient to enhance preference for 5mg/kg cocaine, a dose that does not produce CPP in control males.

We next tested whether the effects of GPER1 activation were specific to cocaine or could broadly attenuate other types of rewarding stimuli. We used a 2-bottle preference with 0.1% saccharin vs H2O and found that males treated with G1, the GPER1 agonist, in the DLS had a significantly lower preference score than CHOL treated males ($p = 0.0411$), indicating GPER1 activation causes a conditioned avoidance for 0.1% saccharin in males. There was no effect of G1 on preference for 0.1% saccharin vs. water in females.

Conclusions: We have identified a novel role of GPER1 within the DLS of male rats to modulate preference for two distinct types of rewarding stimuli. Our results support the notion that activation of GPER1 decreases the preference for cocaine in males, which is

opposite of previous research findings in females where E2 enhances drug preference. Together, these results indicate that E2 could be playing opposing roles in males and females which may explain why females are disproportionately susceptible to addiction.

Our findings also have clinical relevance because they suggest GPER1 activation may be protective in males. Interestingly, one selective estrogen receptor modulator which regulates GPER1, raloxifene, is already used in clinical practice for the treatment of disease. It would be of value to determine if this drug, or others like it, may be useful in the treatment of addiction for males specifically.

Keywords: Sex Differences, GPER1, Addiction

Disclosure: Nothing to disclose.

T194. Chemogenetic Modulation of Pro-Opiomelanocortin Hypothalamic Neurons Alters Ethanol Consumption and Opioid Peptide Levels in a Sex-Specific Manner

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Background: Alcohol abuse is a worldwide public health concern that leads to nearly 90,000 deaths within the United States annually. Activation of the endogenous opioid system is one mechanism by which alcohol may promote its euphoric and motivational effects. Supporting the role of the endogenous opioid system in alcohol abuse, the broad-spectrum opioid receptor antagonist naltrexone is one of the most frequently utilized medications for treating alcohol use disorders. Pro-opiomelanocortin (POMC) producing neurons located within the arcuate nucleus (ArcN) of the hypothalamus make up one particular circuit of the endogenous opioid system, which heavily project to reward-related brain areas. POMC producing neurons are known to release β-endorphin and other peptides previous associated with alcohol consumption. In this study, we aimed to address whether chemogenetic modulation of ArcN POMC neurons can drive ethanol consumption and produce changes in POMC-related peptide levels.

Methods: B6.FVB-tg (POMC-cre)1Lowl/J (referred to as POMC-cre) mice underwent a stereotaxic infusion of cre-dependent DREADD viral vectors directly into the ArcN of the hypothalamus, using either an inhibitory (AAV5-hSyn-DIO-HM4D(Gi)-mCherry), excitatory (AAV5-hSyn-DIO-rM3D(Gs)-mCherry) or control (AAV5-hSyn-DIO-mCherry) DREADD vector. After 4 weeks of recovery, animals underwent 5 consecutive days of drinking-in-the-dark (DID) testing, each of which lasted 2 hr. On day 5, 30 min prior to the initiation of the DID session, animals were injected with clozapine-N-oxide (CNO, 2 mg/kg, i.p.) to either activate or inactivate POMC neurons within the ArcN. One hour following the DID session, crude dissections of the ArcN, nucleus accumbens (NAc), amygdala and ventral tegmental area (VTA) were taken. Tissue samples were homogenized, and western blot analyses were used to assess changes in POMC and β-endorphin expression.

Results: When collapsed across sex, alcohol consumption during the drinking-in-the-dark behavioral task increased across the first 3 days, after which it stabilized. However, when analyzed separately, females showed increased ethanol consumption across sessions, whereas males did not (2-way RM ANOVA; $F3,181 = 10.39$; $p < 0.0001$). Interestingly, chemogenetic inhibition of POMC neurons resulted in increased ethanol intake as compared to following chemogenetic activation of POMC neurons (ANOVA; $F2,44 = 5.7$; $p < 0.01$). and this effect was enhanced in females compared to males (2-way ANOVA; $F2,41 = 6.7$; $p < 0.001$). In Western blot analyses of POMC-derived peptide levels, post-hoc comparisons revealed that inhibition of POMC neurons resulted in enhanced expression of POMC in the ArcN ($t170 = 4.7$; $p < 0.05$), amygdala ($t170 = 5.5$; $p < 0.01$), and NAc ($t170 = 6.4$; $p < 0.001$). Inhibition of POMC neurons decreased β-endorphin expression within the VTA, yet increased expression within the NAc, and these effects appeared to be sex-dependent and were more pronounced in females (2-way ANOVA; VTA: $F1,41 = 1.3$; $p = 0.2$; NAc: $F1,41 = 6.0$; $p < 0.05$).

Conclusions: Here, we have shown sex differences in ethanol consumption throughout the DID behavioral paradigm. Specifically, we report that females display escalation of ethanol intake across DID sessions, whereas males do not. We demonstrate that chemogenetic inhibition of POMC neurons promotes ethanol consumption, an effect that is most evident in female mice. POMC neuronal inhibition resulted in altered POMC and β-endorphin expression in various brain regions, which were more pronounced in female mice. Thus, together these results suggest that POMC neurons regulate ethanol consumption in a sex-dependent manner. Furthermore, POMC neurons may play a sex-dependent role in modulating the underlying circuitry contributing to ethanol consumption.

Keywords: Alcohol, Proopiomelanocortin Neurons, Chemogenetics, Alcohol Drinking

Disclosure: Nothing to disclose.

T195. Characterization of Neurofunctional Domain Measures of the Addictions Neuroclinical Assessment Battery in Alcohol Use Disorder

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Background: The Addictions Neuroclinical Assessment (ANA) is a clinical and translational neuroscience framework comprised of three neurofunctional domains relevant to addiction: Incentive Salience, Negative Emotionality, and Executive Functioning. The ANA battery uses deep phenotyping to better characterize these neurofunctional domains with the goal of obtaining a comprehensive understanding of the etiology and heterogeneity of AUD as well as developing precise and personalized treatments, as well as for detecting efficacy and treatment mechanisms for AUD. Here, we examine the self-report and behavioral task measures within each of the three domains of the ANA battery for relationships with AUD diagnosis as well as with non-ANA measures of impulsivity, impaired control, stress and craving.

Methods: The study included a diverse sample of individuals ($n = 250$) across the spectrum of alcohol use enrolled at the NIAAA clinical research treatment program in Bethesda, MD. Participants completed a comprehensive battery of self-report questionnaires and behavioral tasks assessing the neurofunctional domains of the ANA. Executive function measures included

working memory (Backwards Digit Span Task), spatial reasoning (Manikin Test), reward-based decision-making (Effort Expenditure for Reward Task, EEfRT), and visual attention (Trail Making Task, TMT). Negative emotionality measures included scales of positive and negative affect (Positive and Negative Affect Scale), alexithymia (Toronto Alexithymia Scale-20, TAS), resilience (Connor-Davidson Resilience Scale, CDRS) and distress tolerance (Paced Auditory Serial Addition Task, PASAT). Incentive salience measures included the hypothetical purchase task (HPT) and approach-avoidance task (A-A task). Participants also completed self-report measures of impulsivity, including the Barrett's Impulsivity Scale

(BIS-11), UPPS Impulsive Behavior Scale (UPPS-P), impaired control (Impaired Control Scale, ICS), stress (Perceived Stress Scale, PSS), and craving (Obsessive Compulsive Drinking Scale, OCDS).

Results: Initial analyses focused on examining the effect of AUD diagnosis on the individual measures and demonstrated that the AUD and non-AUD groups differed on nearly all measures. Next, correlational analyses were conducted to examine relationships between measures within domains and with non-ANA measures associated with those domains. For the Executive function domain, only the EEfRT measures were associated with the BIS-11 and UPPS-P, while other task measures correlated only with ICS subscale scores. Linear regression analysis, controlling for age, sex and AUD diagnosis, indicated that the ICS perceived control score (ICS−PC) was a consistent significant predictor across task measures. Specifically, lower ICS−PC predicted a lower proportion of correct responses on the Manikin task ($p = 0.029$) and an increased total time on the TMT ($p = 0.001$). There was also a significant ICS−PC x Sex interaction effect on total time on the TMT ($p = 0.038$). For the Negative Emotionality domain, all the ANA measures, except for the PANAS positive affect scale, were highly correlated with PSS score. Subsequent regression analyses, controlling for age, sex and AUD diagnosis, indicated that higher perceived stress was associated with decreased positive affect ($p = 0.001$) and resilience ($p < 0.001$), and predicted increased negative affect ($p < 0.001$) and alexithymia ($p < 0.001$). Additionally, there was a significant moderating effect of sex on the relationship between perceived stress and resilience, with females showing a steeper negative relationship than males ($p = 0.002$). While PASAT scores differed by diagnosis, regression analysis indicated no significant relationship to PSS score.

Conclusions: These results indicate that, as expected, measures of executive function and negative emotionality differed between AUD and non-AUD individuals. Executive function domain measures were inter-related and significantly associated with impaired control scale measures, specifically perceived control, highlighting the importance of including alcohol-specific measures of control to better characterize the neurofunctional underpinnings of AUD. Negative emotionality self-report measures showed high fidelity with measures of perceived stress, confirming that they are appropriate for assessing this domain. Ongoing analyses are examining inter-relationships for the Incentive Salience domain and associations with craving measures, as well as relationships between measures across domains. These findings add to our evaluation of the ANA battery as a framework for understanding the heterogeneity in AUD based on neurofunctional domains that underlie the neurobiology of addiction. We are trying to determine if the ANA measures can also index variation in progression of dysfunction in AUD, as well as being indicators of risk. Application of this approach to characterize individual differences in risk factors can help provide deeper insights, more accurate assessments and potential targets and mechanisms for treatment and ultimately better outcomes for AUD.

Keywords: Clinical Neurobiology, Alcohol and Substance Use Disorders, Addiction Phenotypes, Negative Emotionality, Executive Function

Disclosure: Nothing to disclose.

T196. Cortical Mechanisms in Relapse to Fentanyl Seeking After Food Choice-Induced Voluntary Abstinence

Abstract not included.

T197. Social Cognitive Performance in Schizophrenia Spectrum Disorders Compared to Autism Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression

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Background: Schizophrenia spectrum disorders (SSDs) and autism spectrum disorder (ASD) both feature social cognitive deficits, which are highly debilitating. These include lower-level processes (e.g. emotion recognition) and higher-level mentalizing processes (e.g. theory of mind), thought to be subserved by partially dissociable neural networks. Overlapping symptoms in SSDs and ASD have long been recognized, particularly in the realm of social deficits. However, despite some studies including both individuals with SSDs and ASD showing similar levels of social cognitive impairment, including lower-level and higher-level deficits, results are mixed. Thus, our objective was to determine based on the extant literature how deficits in social cognition diverge or overlap between individuals with SSDs and ASD by conducting a systematic review and meta-analysis of studies directly comparing these groups on performance-based social cognitive measures.

Methods: Literature searches were conducted in MEDLINE, Embase, PsycINFO, and Web of Science to identify articles that utilized performance-based measures to assess social cognition in both SSDs and ASD samples. Across accepted articles, random-effects meta-analyses were conducted for identified lower-level (e.g. facial and/or context-embedded emotion recognition) and higher-level (e.g. intention understanding, perspective taking) social cognitive measures, and separately for the Reading the Mind in the Eyes test (RMET). Effect sizes were estimated using Hedges' g (SSDs-ASD). Heterogeneity of effect sizes and publication bias were assessed for each meta-analysis. Moderator and sensitivity analyses were also conducted to identify sources of heterogeneity and evaluate robustness of effects.

Results: Of the 4175 screened articles, 36 were included in the qualitative analysis and 33 were included in the quantitative analyses (SSDs $N = 1113$, ASD $N = 1015$). The meta-analyses showed that there were no significant differences between SSDs and ASD groups on lower-level social cognitive measures ($k = 15$, $g = 0.12$, 95% CI [−0.07, 0.30], $p = 0.21$, $I2 = 51.0\%$; one outlier excluded), higher-level social cognitive measures ($k = 17$, $g = -0.01$, 95% CI [−0.21, 0.19], $p = 0.92$, $I2 = 56.5\%$; one outlier excluded), or the RMET ($k = 13$, $g = 0.25$, 95% CI [−0.04, 0.53], $p = 0.095$, $I2 = 75.3\%$). There was no evidence of publication bias. However, heterogeneity of effect sizes was apparent across meta-analyses and was only minimally explained by explored moderators. Sensitivity analyses confirmed robustness of findings.

Conclusions: Based on meta-analyses of the extant literature, similar levels of social cognitive impairment may be present in SSDs and ASD, across lower- and higher-level social cognition. However, there was considerable between-study heterogeneity in social cognitive performance differences between SSDs and ASD groups. The included studies highlight the prevalence of small, male-predominant samples, and a paucity of clinical measures across SSDs and ASD groups. Cross-disorder studies probing social cognitive domains with larger samples, consistent reporting of clinical measures, and neuroimaging are needed to substantiate these findings, clarify underlying mechanisms, and parse heterogeneity.

Keywords: Meta-Analysis, Social Cognition, Schizophrenia Spectrum Disorders, Autism Spectrum Disorder, Systematic Review

Disclosure: Nothing to disclose.

T198. Biological and Environmental Distinctiveness of Data Driven Dimensions of Psychopathology in the Adolescent Brain and Cognitive Development Study

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Background: Identifying dissociable dimensions of psychopathology with distinct neurobiological and environmental underpinning is challenging but important, because it offers an opportunity for more targeted intervention. In the present study, we aimed to Identify data-driven dimensions of psychopathology that are maximally dissimilar to each other and to characterize their distinct neurobiological, individual, and environmental signatures.

Methods: We used data from the baseline visit of the ABCD study, a prospective longitudinal Multicenter population-based cohort. The study participants were 11875 individuals age 9–10 who were selected through multi-stage probability sampling and were representative of the US population. We conducted independent component analysis (ICA) on items of Childhood Behavior Checklist to identify maximally dissimilar dimensions of psychopathology. The optimal number of components were found using stability and leave-one-site analysis. We further tested the association between individual, environmental and functional and structural brain organization and the resulting dimensions using both linear and nonlinear modeling. We further compared these data-driven dimensions with precomputed CBCL subscales and syndrome scales derived from factor analytic solutions.

Results: A total of 9983 subjects from 9983 unique families (47.8% female, 50.8% white) were selected for the analysis. We found three highly stable and distinct components representing oppositional behavior, cognitive dyscontrol, and negative affect (Stability = 0.9, range = 0.85–0.92). Despite sharing important risk factors such as trauma, parental psychopathology, and financial difficulties, the ICA-driven components were neurobiologically distinct with respect brain structural and functional organizations and were separable on demographic, psychological, cognitive, and environmental factors. This distinctiveness in neurobiological and environmental signature of psychopathology was attenuated or absent in CBCL precomputed subscales.

Conclusions: Using a data-driven approach and linear and nonlinear modeling, we found separable psychopathological components with distinct individual, psychosocial, and neurobiological signatures and different patterns of sensitivity to environment and brain-environment interactions. Findings of the present study can enhance our understanding of the neurobiological underpinning of psychopathology while at the same time providing new avenues for targeted prevention and treatment strategies.

Keywords: Adolescent Brain Cognitive Development Study, Human Neuroimaging, Child Psychopharmacology

Disclosure: Nothing to disclose.

T199. Does Transcranial Magnetic Stimulation Work Through Synaptic Plasticity?

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Background: Repetitive Transcranial Magnetic Stimulation (rTMS) is a safe and effective treatment for depression, and potentially for numerous other neuropsychiatric disorders. While the utilization of rTMS is advancing rapidly, it is without a clear mechanistic understanding of how TMS changes the brain. We hypothesized that high-frequency (HF)-rTMS (such as 10 Hz protocols commonly used in clinics) may enhance the strength of synaptic connections between neurons coming from the prefrontal cortex through long-term potentiation (LTP), a form of synaptic plasticity. We previously reported that NMDA receptor partial agonist, d-cycloserine, was sufficient to enhance potentiation in motor-evoked potentials (MEPs), a measure of cortical excitability. In the same subjects, we sought to further test the role of NMDA-receptor dependent LTP in HF-rTMS using paired-pulse protocols, Intracortical Inhibition (ICI) and Intracortical Facilitation (ICF), which enable examination of relative GABAergic and glutamatergic contributions, respectively.

Methods: Ten healthy participants aged 18 to 50 (6 male) were randomized into a double-blind, crossover pilot study comparing the effects of 100 mg d-cycloserine (DCS), an NMDA receptor partial agonist vs. placebo on motor evoked potentials (MEPs) before and after 300 pulses of 10 Hz rTMS (1.5 sec on/58.5 sec off) over the left motor cortex at 80% motor threshold. Baseline ICI/ICF measures were taken prior to rTMS, and 1 hour after drug administration to account for effects on baseline excitability. The rTMS 'plasticity protocol' was administered 2 hours after placebo or DCS capsules were given orally. Post-TMS ICI/ICF measures were obtained within 30 minutes following rTMS. Visits were at least 1 week apart for drug wash-out. ICI and ICF are both calculated by dividing the paired-pulse MEP amplitude by the single-pulse MEP amplitude to produce a percent change (PC). Post-rTMS PC is subtracted from Pre-rTMS PC. These values are compared statistically with Wilcoxin sum-ranked test, with-in subjects between each drug condition. ICF interstimulus interval (ISI) was 15 ms and ICI ISI was 3 ms. The initial subthreshold pulse is at 80% resting motor threshold (rMT) and the second suprathreshold pulse is approximately 120% rMT, or calibrated to evoke a 1 mV MEP.

Results: ICF was inhibited in the DCS group relative to placebo. Average PC values before and after rTMS in the placebo group were 24.875 and 60.445; compared to 55.939 and 21.118 in the DCS group; $p = 0.037$, effect size = 1.050. ICI was further inhibited in the DCS group relative to placebo. Placebo values before and after rTMS were -62.34 and -37.351 compared to -44.237 and -70.615 in the DCS group, $p = 0.027$; effect size = 1.066.

Conclusions: In a small sample size of ten healthy subjects, ICF was blunted and ICI enhanced. While interpretation of a small study should be approached with caution, these unexpected results could be explained by homeostatic plasticity. In this case, the superimposed potentiation from DCS and HF-rTMS may induce, but still outweigh, increased GABAergic tone. Thus, despite a net positive MEP (published previously), when elicited by a short-term plasticity protocol designed to isolate GABAergic inhibition (like ICI), the isolated inhibition would be enhanced. In this case, residual GABAergic tone might still be present at 15 ms, when GABA neurotransmission should have been dormant, thus counteracting or even reversing the facilitation protocol. Replication and extending the ISI are necessary next steps.

Keywords: Synaptic Plasticity, Repetitive Transcranial Magnetic Stimulation (rTMS), NMDA Receptor, GABA-A Receptors, Motor Evoked Potentials

Disclosure: Nothing to disclose.

T200. Default Mode Network Remodels Frontoparietal Network in Self-Referential Task

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Background: Default mode network (DMN) is a large-scale brain system originally characterized by neural deactivation during goal-directed tasks and relative activations in "task-negative", or resting

states. Recent works challenge this antagonistic framing, showing that internally directed cognitive tasks can produce greater DMN activation than at rest. This DMN activity is associated with task-linked coupling between DMN and the frontoparietal control network (FPCN), a brain system implicated in guiding goal-oriented cognition. Additional work suggests FPCN has subsystems specializing in externally vs. internally directed tasks, the latter being relatively under-studied. We added to this effort to map internally directed cognition through network analysis of an exemplar internally directed task.

Methods: Using functional magnetic resonance imaging in 27 healthy subjects, we examined DMN and FPCN within- and between-network connectivity in the context of an internally cued self-referential task compared to an externally cued control counting task.

Results: Self-referential thoughts increased within-network connectivity in DMN ($F = 3.7$, $p < 0.04$) while disrupting it in FPCN ($F = 23.2$, $p < 8 \times 10^{-8}$). This disruption was associated with a subset of FPCN coupling with DMN. Data-driven characterization of the FPCN subcomponent revealed pronounced left lateralization ($p < 0.002$, $z = 37.3$).

Conclusions: Self-referential cognition increased connectivity within DMN and between DMN and left-lateralized cognitive control regions in FPCN. This task-dependent network coordination may inform the future study of neuropsychiatric conditions where altered DMN or FPCN connectivity has been implicated, including autism, depression, migraine, and psychosis.

Keywords: Functional MRI (fMRI), Default Mode Network (DMN), Autobiographical Memory

Disclosure: Nothing to disclose.